The Journal of the
American Medical Association

VOL XXII CHICAGO, APRIL 7, 1894 No 14

LECTURE

OOPHORECTOMY AND UTERINE CURETTAGE UPON THE SAME PATIENT—INTERSTITIAL SALPINGITIS—HEMATOMA OF THE OVARY, AND PELVIC PERITONITIS—DIAGNOSIS UNDER ANESTHESIA

A Clinical Lecture delivered at St. Luke s Hospital

BY HENRY T BYFORD, M.D

CHICAGO

PROFESSOR OF GYNECOLOGY COLLEGE OF PHYSICIANS AND SURGEONS, PROFESSOR OF GYNECOLOGY CHICAGO POST-GRADUATE MEDICAL SCHOOL
PROFESSOR OF CLINICAL GYNECOLOGY, WOMAN'S MEDICAL
COLLEGE GYNECOLOGIST TO ST LUKE S HOSPITAL
SURGEON TO WOMAN S HOSPITAL OF CHICAGO
CONSULTING GYNECOLOGIST TO MICHAEL
REESE CHARITY, CHICAGO, AND
PROVIDENT HOSPITALS

Diagnosis —The case represented by the patient now being anesthetized might, in the slang phraseology of the past decade, be called a "chestnut"—it is a case of oophorectomy for diseased uterine appendages We have lately had a case of oophorectomy at almost every weekly gynecologic clinic You might justly make the criticism that were I a man of parts I would ring a few changes in these cases, and do something for them besides eternally taking out the ovaries, more particularly since it is now the fashion to treat the endometrium and even to remove the uterus and let the diseased ovaries and tubes remain Yet I expect to find something interesting and instructive even about this every-day case

The young lady is a nulliparous grass widow 25 years old, who has made me promise to leave one ovary She has been up and down with slight attacks of peritonitis for five months She has been faithfully but unavailingly treated, and demands a cure She has also a muco purulent endometritis which, with other facts, suggests a possible gonorrheal origin There is a profuse menorrhagia for a week of each month and a moderate metrorrhagia coming and going from one to two weeks thereafter

I first proceed to curette the uterus I find the cervix purplish, the subject... nal os soft and dilatable to the size of a few histologic... the blades of Goodell's dilator The one which I use flabby and the mucous and submucous tissues infiltrated The blades of the dilator being separated three fourths of an inch I scrape out the softened mucous membrane until I can get no more, being careful not to injure the softened muscular tissue Having washed out the uterine cavity with a 1-2000 solution of bichlorid of mercury, I swab it out with a 95 per cent carbolic acid, and consider that we have relieved the uterus of its portion of the sepsis

I disinfect my hands again, while the nurses are arranging the patient for an abdominal section

A small low incision in the linea alba reveals some frail adhesions of an almost normal ovary and tube on the right side, which I have broken up before lifting the parts to the surface for inspection On the left side the omentum is firmly adherent to the horn of the uterus The adhesions are recent, for the tissues are still blackish with unabsorbed minute extravasations of blood This blackened appearance of the omentum does not denote rottenness, as many hasty observers are apt to infer I tie it off only far enough to head off the oozing, and shall expect the tissues to present a normal appearance within a few weeks, as I have verified by secondary operations in other cases The tube is the size of the finger and with its adhesions presents a typical case of an interstitial salpingitis The ovary is the size of a small egg, and is embraced by the tube and so firmly adherent to the posterior surface of the broad ligament that I can separate it only with the greatest difficulty. I have walled off the intestines by sponges, for fear that pus may be present and that it might escape as the adherent tissues separate The mass comes up without rupture, however, and I proceed to ligature the appendages as close to the uterus as possible, in order not to leave a septic focus at the uterine horn. The adhesions were not very old, the oozing is therefore mostly by capillary and is ceasing so rapidly that I can close the abdominal cavity without drainage

We have now cleaned and disinfected the uterus, removed all of the remaining tissue that contained the septic material and "saved the other ovary and tube harmless" from all liability to infection

An incision into the thickened and yellowish walls of the tube shows it to be filled with thickened mucous membrane and luxuriant vegetations, rather than pus and granulation tissue The fimbriated end is contracted and apparently closed, although not firmly Undoubtedly some fluid had escaped into the abdominal cavity, causing the inflammation and adhesion of the ovary The uterine end admits a large probe and has allowed of drainage, and had it not been for the ovaritis and peritonitis, the patient might, after a long time, have recovered sufficiently without the peritoneal section From the ovary I turn out an organized blood clot the size of a large English walnut The ovarian stroma appears to be pretty well destroyed by interstitial inflammation

This case illustrates in an interesting way the progress of gynecologic surgery Ten years ago this progress was largely made up by the invention and perfection of new operations, during the past five years, however, quite a little of this advance towards perfection has been due to the combination of operations Fifteen years ago we were taught not to perform trachelorrhaphy and perineorrhaphy at the same time, because hemorrhage might take place from the cervix, or the cervical stitches might become infect... and we could not then get at the

wound Pretty soon, however, we began to perform both operations at one sitting, and before long added curetting and the ligature of hemorrhoids to them,—and now this combination (the so-called *big four*) is one of the common procedures in this clinic Later, Alexander's operation was added to this combination, and still later abdominal section Five or six years ago I was afraid to touch the endometrium when I opened the abdomen, and did not dare to open the abdomen immediately after curetting the uterus But antisepsis has taught us that we can do all things in surgery We now operate all over the patient, and her system does not seem to be at all inconvenienced by it

In a month I will make a speculum examination in this case, and see to it that the cervix does not subsequently contract so as to prevent uterine drainage If necessary I will dilate the cervix and apply disinfectants and alteratives to the endometrium until no trace of endometritis shall be left If that is not enough I will again curette, for the only way to "save the other ovary harmless" is to cure the endometritis

Our other patient, who is a virgin, 17 years old, has been sent to me with the supposition that she has serious pelvic trouble Abdominal enlargement, iliac dullness, swelled feet, amenorrhea for a year, cough and palpitation, are the signs and symptoms reported She is anemic, yet quite fleshy and hearty in appearance By pressing over the pubes I bring the abdominal walls well down into the pelvis, and will press upward from the vagina and rectum, and thus bimanually palpate all that is in the pelvis The vagina is small and does not allow of satisfactory palpation of the deeper parts With two fingers in the rectum passed up behind the cul-de-sac of Douglas I penetrate, as it were, right into the pelvic peritoneal cavity and can feel everything But I feel nothing worthy of note The uterus is small and normal, the tubes feel like folds of membrane, the ovaries are a trifle large, but movable and evidently not seriously diseased Instead of diagnosing the case I must undiagnose it The abdominal enlargement was due to intestinal gas, the iliac dullness to feces in the sigmoid flexure, and the amenorrhea, swelled feet and palpitation to cardiac complications and anemia We will turn the patient over to the medical department The medical attendant will examine her heart, urinary secretions and other functions, inquire into the diseases of her infancy, etc, and will undoubtedly find something to do for her besides removing the ovaries

When you go out to practice I hope that before sending in cases for gynecologic operations you will examine into general conditions, and not send patients suffering with mitral regurgitation or chronic nephritis to a gynecologist to run the risk of having their unoffending ovaries removed Remember, also, that if it is necessary for me to give an anesthetic to clear up a diagnosis of pelvic trouble, that you yourselves might profit by adopting the same procedure

DELAYED DELEGATION —Dr A Jacobi, of New York, chairman of the American delegation to the Rome International Medical Congress, has telegraphed that his departure was delayed, and in consequence he and a number of other American physicians were unable to be present at the opening of the Congress. Dr Jacobi added that he and his party expected to arrive in Rome before the final adjournment of the Congress —*N Y Herald*

ORIGINAL ARTICLES.

POSTERIOR PROSTATO-CYSTOTOMY

BY WILLIAM T BELFIELD, M D
CHICAGO

Of the various operations that have been practiced for reaching the bladder and prostate, only the median perineal and supra-pubic continue in general favor, and since the usefulness of the former is for anatomical reasons greatly restricted, the supra-pubic almost monopolizes the field

The operation of Kraske for extirpation of the cancerous rectum has suggested to various surgeons a method for reaching important structures at the posterior surface of the bladder Ullmann removed a tuberculous seminal vesicle, Dittel proposed and Kuster executed the post-urethral excision of lateral masses of the enlarged prostate, Cabot suggested the extraction of ureteral calculi, and the present writer drained a suppurating prostatic utricle As the result chiefly of anatomical studies, I now venture to call attention to an operation that may be described as *posterior prostato-cystotomy*

The anesthetized patient is placed upon the left side, thighs flexed to a right angle, hips elevated eight inches or more, rectum empty and bladder moderately distended with air, a broad grooved staff is introduced From a point midway between the tip of the coccyx and the right tuber ischii a superficial incision is carried forward, curving toward the raphé which it reaches one and a half inches in front of the anus Guided by a finger in the rectum and the staff, blunt instruments carefully dissect the rectum from the membranous urethra, prostate and bladder-wall between the lower extremities of the vesicles The rectum being held out of the way by a retractor (it would be desirable here to ligate on each side the prostatic venous plexus, if unusually large) the point of a knife is made to enter the groove of the staff exactly in the median line half an inch above, and is carried downward to a point the same distance below, the upper border of the prostate, dividing the trigone, the so-called "middle lobe" of the prostate, and the prostatic utricle, and terminating just above the orifices of the ejaculatory ducts If required, the incision can be safely extended in the median line upward half an inch and downward through the thin commissure joining the lateral lobes of the prostate

When the divided edges are drawn apart, the entire prostatic surface is accessible to eye and finger, the bladder can be drawn downward and the ureteral orifices exposed (on the cadaver) Complete suturing of the wound in bladder and prostate, while practicable, would probably be less desirable than partial suturing and drainage through the upper angle of the wound, which corresponds with the lowest point of the contracted bladder [1]

This incision seems to have two decided advantages over the supra-pubic 1, perfect command of the entire prostate and base of bladder and, 2, perfect drainage and consequent reduction to a minimum of the dangers of urinary infiltration, it is also practicable in cases of contracted bladder to which the supra-pubic is not adapted Incidentally it affords access to structures whose intimate clinical relations with bladder and prostate are becoming better understood—prostatic utricle, seminal vesicles and extremities of ureters, for reaching the fundus of the bladder, however, it seems inferior to the high incision

The proper field of this operation must be shown by extensive clinical experience, I have used it in one case, removing a calculus and lateral masses of

[1] It might be found possible to introduce suitable catheters into the ureters and thus prevent contact of the urine with the wound, whether this difficult measure would have any practical advantage over the perfect low level drainage afforded by the tube seems doubtful

the enlarged prostate, the latter being far more accessible than I have ever found them through the supra-pubic incision Complete healing followed in fifteen days

A New Method for Drainage of the Bladder—Perfect drainage of the bladder is obtained by a simpler incision along the same route A tenotome is made to enter the perineum—blade horizontal—an inch or more in front of the anal margin, passed between prostate and rectum, and enters the bladder between the upper extremities of the prostatic lobes (it is well to have the bladder partly filled and its floor depressed by the beak of a sound), a slender forceps is carried along the blade into the bladder, the knife removed and the channel dilated by separation of the branches of the forceps for the introduction of the drainage tube This incision opens and drains the prostatic utricle—which appears to be an important factor in prostato-cystitis from any cause I have used this method of drainage in two cases with entire satisfaction The perfection of such drainage was well shown in a third case, operated by Dr Wishard, of Indianapolis, concerning which the writer was consulted To prevent urinary contamination of a plastic operation for remedying a complete epispadias in a man 22 years old who had absolutely no vesical sphincter and consequently complete incontinence, a soft catheter was introduced through this incision The bladder was kept so thoroughly empty that the flaps ingeniously made to cover the deep urethra healed by primary union

THREE CASES OF CARCINOMA DEVELOPED ON LUPUS VULGARIS

Read before the Chicago Pathological Society Feb 13 1894

BY EMANUEL FRIEND, M D

CHICAGO

CHIEF ATTENDING PHYSICIAN TO DEPARTMENT OF SKIN AND GENITO URINARY DISEASES UNITED HEBREW CHARITY DISPENSARY, ATTENDING PHYSICIAN TO CENTRAL FREE DISPENSARY

It is a well-known fact that when two or more ulcerating affections of the external skin of different etiologic relations, involve the same region, they often give rise to great difficulty in making a diagnosis

Such cases, for instance, as the combination of syphilis and carcinoma reported by Lang and Doutrelepont, others again as lupus and carcinoma first reported by O Weber in 1859, and following him came Esmark, Hebra, Lang and numerous others

Having been afforded during my last year's stay in Vienna, of seeing at least three cases of carcinoma developed upon the site of lupus vulgaris of the face, I take the liberty of giving you a brief *résumé* of the scanty literature of the subject, and at the same time demonstrating a few histologic specimens relating to the subject The one which I have at present under the microscope, having been used by Prof Kaposi while lecturing on this subject last winter, the others I prepared since my return home

Ziegler, *Allegemeine und Specielle Pathologische Anatomie*, page 465, under "Epithelial New Growths" states "The epithelial hyperplasia may take place in the epidermis, as well as the epithelium of the sebaceous glands and the hair follicles, probably also the sweat glands"

In the epithelial papillæ of many of the cancers involving the skin, there are found lamellated nodules of horny epithelium, and in consequence they have received the name of horn cancers Occasionally calcification takes place in such cancers

Page 466 "The epithelial cancers, that is those growing out from the rète malphigii, develop with preference at the junction of the external skin and the mucous membranes, on the lower lip, nose, eyelids, preputium, anus, external female genitals, etc Sometimes they start from warts, cornu cutaneæ, scars, pustules and ulcers, and arise not seldom upon the base of a lupus ulcer or scar"

Neisser, *Ziemssen Pathologie and Therapy*, Vol xiv, page 606, in his "Differential Diagnosis" between lupus vulgaris and carcinoma, says, "one ought not to forget that complications of carcinoma and lupus occur, and in these cases owing to lack of resistance, in part, of the lupus tissue against the encroaching cancer papillæ, it is advisable to adopt early therapeutic measures"

Lesser, *Lehrbuch der Haut und geschlects Krankheiten*, page 201, states "Occasionally pathologic changes in tissue are the seat of epithelial carcinoma, which are in no way directly responsible for the origin of same, such as ulcers of foot, syphilitic ulcerations, lupus, etc'

The probabilities are that the pathologic epithelial proliferations in connection with the diminished resistance of the connective tissue are responsible for this atypical hyperplasia, the formation of cancer

The technique of preparation of the specimens was as follows The excised piece of tissue was hardened in alcohol, beginning at 60 per cent and increasing gradually to absolute alcohol Then put in equal parts of ether and alcohol for two or three days and, finally, from a thin solution of celloidin to a thicker one and then mounted and cut, the sections being about fifteen micromill thick Hamatoxylin and eosin used as stains A number of sections I stained by both Ziehl and Kuhne's method for tubercle bacilli with negative results, which did not surprise me, as you all know how rarely the bacillus is found in lupus tissue, possibly once in 90 or 100 sections, and on this very ground is largely based the argument for the non-tuberculous nature of lupus vulgaris, by a few of the leading dermatologists and pathologists of Europe

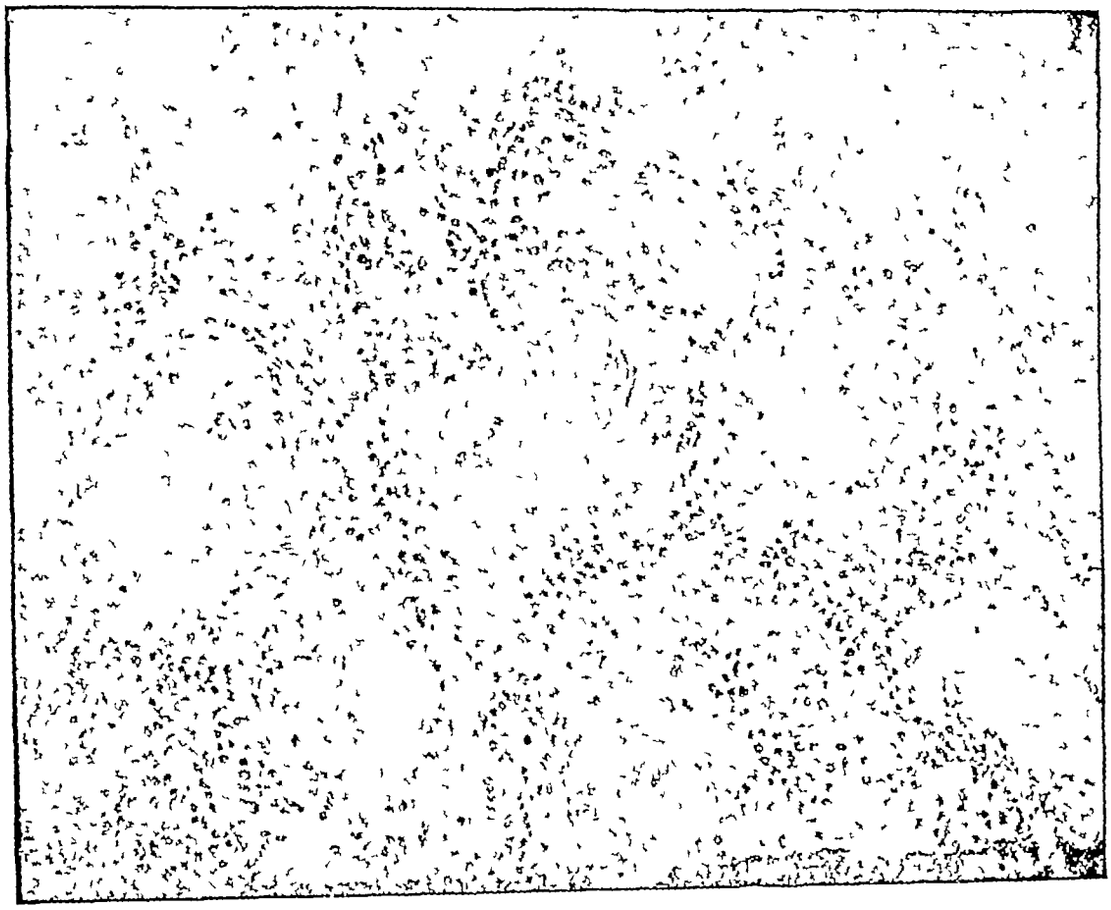
Microscopic Picture—Zeiss A Ocular No 3 One sees deep in the corium, isolated tissue masses called by Leloir, "Lupome" They lie irregularly and at different depths in the corium, while the upper and papillary layer, and rète malphigii appear normal, and at the same time one sees, below and interspersed in these so called lupome nodules, are some round, others elliptical bodies, which have taken the eosin stain more readily than the surrounding tissue, the extreme vascularity of the part is very noticeable

Zeiss E Ocular 3, shows how well defined the borders of the lupus nodules are from the surrounding connective tissue, although slightly more irregular in their arrangement they are made up of the same constituents as the miliary tubercle, namely granulation tissue, epitheloid and giant cells The main difference between the lupus nodule and the tubercle, being the retrograde metamorphosis which they undergo, while in the tubercle we get a typical cheesy degeneration in the lupus nodule we get more an atypical or fatty degeneration, while the interstitial connective tissue becomes hyperplastic and contracts

The difference in the retrograde metamorphosis is said by some to be due to the vascularity of lupus in contra-distinction to the tubercle, while others again believe the relative number of tubercle bacilli responsible for the difference

undergone a kerato-hyaline degeneration These are undoubtedly epithelial nests, some cut diagonally, others cut square across

In the three cases, which I saw in Prof Kaposi's wards, the face was the seat of the affection, whether



The round and elliptical bodies previously mentioned are now seen to be made up of concentric layers of cells, with few nuclei, the whole or rather the more central parts with the appearance of having

or not this is the most common seat, I have been unable to determine, but judging from the fact that the face is the most common seat of lupus vulgaris, it would be plausible to consider the face as the most

common seat of this complication, with carcinoma [In conclusion, I wish to thank Prof Paltauf, as well as Docent Riehl for their liberality in supplying me with material, as well as for the many other kind favors shown me during my studies in Vienna

PRACTICAL POINTS IN TREATING DISEASES OF THE EYE, EAR, NOSE AND THROAT

Read before the Dauphin County Pennsylvania, Medical Society, March 6, 1894

BY J WALTER PARK M D

HARRISBURG, PA

OPHTHALMIC SURGEON TO THE HARRISBURG HOSPITAL, CHILDREN'S INDUSTRIAL HOME AND HOME OF THE FRIENDLESS LATE CLINICAL ASSISTANT ROYAL LONDON OPHTHALMIC HOSPITAL, LONDON, ENGLAND

The professional relationship existing between the general practitioner and the one who confines himself to special branches of medicine, is one of such a character that the constant interchanging of views upon practical points, gained by experience in the various branches of medicine, is of so much importance that I will endeavor to present for your consideration to day, a few practical points, of such a character as will interest the general profession more than it will my esteemed colleagues, who limit their work the same as I do We will consider them in the following order 1, the eye, 2, the ear, 3, the nose, 4, the pharynx and larynx

1 *The Eye*—It is well that there should be some methodical way in examining a patient when he presents himself for examination, it is therefore your first duty to take a general view of the eyes to be examined, observing the movability of the eyeballs in their various meridians, to see with what freedom and to what extent he can move the various recti muscles in all directions, the condition of the eyelids, lachrymal puncta, ocular and palpebral conjunctivæ, the transparency of the cornea and the movability of the iris In an inflamed eye always be sure to look for a foreign body, either in the cornea or under the lids, this can not well be done without the f a lens to concentrate the rays of light upon parts to be examined by artificial light and an thalmoscope The latter are often imperative to amine the movability of the iris Occasionally u will find a short, inverted, white cilia on the pper or lower lid near the inner canthus, and seemngly prodding into the caruncle, which if removed will remedy the entire inflammatory condition Next of importance to foreign bodies in the eye, is the movability of the pupillary border of the iris Generally you will find a change in its color when any inflammatory condition exists, but quite frequently in the early stages this change has not taken place sufficiently to be visible to the eye, hence the necessity of depending entirely upon the contraction and dilatation of the pupil by artificial light concentrated upon the cornea, by the aid of which you can readily discern its movability If immobile, or acting sluggishly, you should instill a mydriatic at once to cause dilatation and prevent adhesions of the iris to the anterior capsule of the lense, for once permanent adhesions form, your chances for good vision are very few indeed To know when and how long to skilfully use a mydriatic, can only be acquired by a long and continued use of the same in diseases of the iris A safe rule to be governed by in the use of atropin, is to never use it in adults over 40 years of age, except in inflammatory diseases of the iris, and then carefully watch the tension of the eyeball for fear that much dreaded disease, glaucoma, may be brought on by its use Use it sparingly and only long enough to keep your pupil dilated

One of the most serious diseases of the eyes to which I can call your attention, is ophthalmia neonatorum When called to see a case of this kind, or one simulating it, the first step taken in examining your case is the most important, that is to examine the child's eyes carefully so as to see the exact condition of the cornea Do not be satisfied with merely *trying* to see its cornea, but be sure you do see it Every physician should have a pair of small lid retractors, for without them you can not get a good view, on account of the severe blepharospasm, and the cornea always rolling up under the lids, out of sight Thorough antisepsis in every particular is necessary A detailed account of its treatment in this paper would consume too much of your time, but a few words as regards the use of atropin, I think, are necessary Atropin should always be used if you have an ulcer in the center of the cornea, and eserin in its stead for the marginal ring ulcer This ulcer often starts at the sclero-corneal junction, and in forty eight hours has traversed the entire border of the cornea The eserin contracts the pupil and by its tension on the iris prevents prolapse into the perforating ulcer, while a *similar condition* is prevented, by *dilatation* of the pupil, when the ulcer is central Phlyctenular keratitis, or the small and multiple ulcer of the cornea is another frequent disease of children, and one of the most common diseases of childhood Photophobia, the almost constant and contracted condition of the eyelids often a papular eruption around the eyes, and an acute or chronic rhinitis are its chief symptoms Note this fact, that most cases are preceded by a running nose, or in other words, an acute or chronic rhinitis, bad sanitary condition of their habitations, an insufficiency of the proper kind of food, and that if you treat the nose, administer good food, the daily bath, etc, in *conjunction* with the treatment of the eyes, your patient will get well in half the time that is required if you only treat the eyes, and neglect the nasal complication

If you only treat the eyes, and neglect the nose, you will generally have successive crops of phlyctenular ulcers return, and the result will be that you have your patients on your hands for a long time, and perhaps lose them, by their getting into other hands

Atropin and yellow oxide of mercury are the best remedies for these cases Boracic acid solution injected into the nostrils will generally remedy the rhinitis in children Persistent treatment, however, must be enjoined upon the patients even after they are seemingly well The general health, as well, must be attended to in all cases, as a rule

2 *The Ear*—Next of importance is the organ of hearing Quite an advancement in the treatment of diseases of the ear has been made within the past five to ten years The most satisfactory, however, has been the removal of the ossicles and tympanic membrane for chronic suppuration of the middle ear Where there are no mastoid complications, eight out of every ten cases of from six months' to three years' standing, that have resisted all other forms of treatment, get well after this operation, if it

is well and properly done The removal of the stapes is rarely required Quite frequently, in old or chronic cases, there are no ossicles to be found, they having been entirely destroyed by suppurative processes Where the hearing in suppurative cases is defective, about 50 per cent of the cases are improved Tinnitus aurium is also most always greatly relieved and generally entirely stopped

I have lately been using Dr Doench's middle ear apparatus for the purpose of applying medicated vapors in the middle ear for chronic catarrhal deafness, and find that when menthol vapor is thus introduced through the Eustachian catheter, I can invariably improve cases of from six months' to two years' standing, who hear the tick of an ordinary loud ticking watch at three inches, to fifteen and twenty inches by actual measurement The tinnitus aurium is also almost entirely relieved in a majority of the cases The operation for the removal of the ossicles is very simple, and usually does not confine your patient to bed over forty-eight hours, almost *always* unattended with any danger, and usually in four or five days is attending to business again When you have a chronic, fetid suppurating ear, with tenderness over the mastoid process, there is generally mastoid complication, and the earlier you establish free drainage by either opening it up through the attic of the tympanic cavity, or the mastoid process, the sooner your patient will get well Chronic suppurating ears, sooner or later, become dangerous to the patient, and contrary to the advice of some physicians, should not be encouraged, but stopped as soon as possible In all acute and chronic suppurating ears, pyoktannin will often arrest the discharge quicker than boracic acid if it is always used in fresh solutions, not over three to five days old I use it in 1 to 500 strength solutions, and find it to have a more *lasting effect* in the destruction of pus germs, than peroxid of hydrogen Wherever there are unhealthy granulations, or symptoms of polypi, there is nothing so efficacious as the curette, followed by equal parts of iodoform and boracic acid blown into the ear twice daily In all acute or chronic suppurating ears, never forget that in *a majority of the cases*, they originate from some acute or chronic pharyngeal or nasal inflammation, that they need watching, and in most instances treatment, before the ear complication will get well Furuncle of the meatus is a very painful and often stubborn disease to treat There is very frequently a tendency to recurrence, and my experience has been that a 40 grain to the ounce solution of menthol in olive oil, generally prevents the recurrence of a second one

3 *The Nose*.—There is no doubt that the nose is one of the most abused organs of the human body Its functions of breathing, smelling, warming and sifting the respiratory air from microorganisms previous to its entering the lungs is very frequently interfered with and imperfectly performed owing to the few *perfectly* formed noses, as well as the *few* which are not diseased in some manner Always be sure to make a careful examination before expressing an opinion In the so called "mouth breathers," you will generally find one of the five following causes for this defect, viz Hypertrophied tonsils, adenoid vegetations in the vault of the pharynx, hypertrophy of Luschka's tonsil, hypertrophy of the turbinated bodies, or nasal polypi If either of these defects exist, the earlier you remedy the cause, the sooner you relieve your patient, and save many complications which may arise by continuous delay The relationship existing between aural and nasal diseases are such that I never think of examining the one without the other Influenzas and catarrhal diseases of the nose and naso-pharynx are the causes of three-fourths of all aural diseases

Stenosis of either nostril, when due to hypertrophied conditions of the turbinated bodies, to exostoses or enchondromas, should always be remedied by operative measures, for it is the only sure way to remedy such defects, restore the natural respiratory functions of the nose, and thereby save many laryngeal and pharyngeal complications which are sooner or later sure to occur Thorough cleanliness of the nose and naso-pharynx, the early recognition and treatment of acute and chronic rhinitis, will generally prevent the hypertrophic conditions, as well as all the aural complications, of which there are so many The early treatment of the hypertrophic form, generally prevents the atrophic variety, which so often follows if this is not done, and once this form is thoroughly established, prevention of its further progress is all that can be done in the way of treatment To even remedy the stench that accompanies atrophic rhinitis requires the constant and close attention of the physician, as well as the patient Of all the various cleansing lotions which I have tried, the boracic acid, sodium chlorid, acid carb and water solution is the best This should be used in all fetid catarrhal conditions, as well as acute and chronic rhinitis, by spraying the nose and naso-pharynx, both anteriorly through the nose and posteriorly through the mouth Fluid petroleum, combined with the various antiseptics, are excellent for the prevention of crust formations, and to allay the stench in most all cases My experience has been that the fluid petroleum for constant use is better adapted for the mucous membrane of the nose than albolene or benzoinol The two latter, after long and continued use, seem to leave a dry condition of the mucous membrane, which the former does not do so much after its discontinued use The fluid petroleum and its combinations should always be used after the cleansing lotion has been used Nasal polypi should always be removed by the snare, and *not* twisted off as is so frequently done After their removal the bases of each one should be thoroughly cauterized, and quite frequently you will not have any return of them, if not done, they will be sure to grow again

Dull headaches and pains in the region of the frontal sinuses, especially when accompanied by dullness of the mental faculties, are generally caused by an extension of the inflammatory conditions in the nose to the frontal sinuses By treating the nasal cavities and establishing free drainage through the ethmoid cells you remedy all the pains, and restore the stunted memory I remember two cases of that nature, whose minds were bordering on insanity, entirely restored by relieving the pent up secretion in the frontal sinuses, caused by immense hypertrophies of the superior and inferior turbinated bodies *Remember*, that a constant dull pain at the base of the nose, and a stunted memory are its chief symptoms If you are not careful you will attribute this pain to some ocular trouble, when in fact it is entirely nasal I have had cases referred to me quite frequently to treat the ocular trouble, when I found it nasal

4 *Pharynx and Larynx*—In examining the pharynx and larynx, considerable skill and dexterity in the manipulation of instruments is required, in order to see and examine the parts well Practice alone, will bring about these results There are plenty of ordinary cases which would never get into the hands of the specialist if you were to devote more time to skilfully handling the laryngoscope and post nasal mirrors A chronic follicular disease of the tonsils which is generally recognized by small, white, cheesy masses imbedded or protruding from the follicles of the tonsils and which invariably taints the breath, is best remedied by puncturing each follicle with the galvano cautery point There is no other treatment so effectual as this Where hemophilia exists, the treatment of hypertrophy of the tonsils is also best done by the galvano cautery point It is really dangerous to practice excision in such cases, while in others where no idiosyncrasy exists, it is the quickest, and equally as effective as the galvano-cautery point In all so called "mouth breathers," look for enlarged tonsils, and adenoid vegetations in the vault of the pharynx Specific ulcers of the tonsils arches of the palate or the walls of the pharynx, yield best to applications of chromic acid, in conjunction with your constitutional treatment

I have used various cauterizing applications, but find none so efficacious as chromic acid In acute and chronic pharyngitis a solution of from 20 to 60 grains to the ounce of nitrate of silver applied twice a week, for awhile, acts admirably Do not be afraid to use strong solutions, for they are generally well borne, and you accomplish in a week's time what would otherwise require a month's treatment In tubercular ulcerations of the pharynx and larynx, the application of the curette and lactic acid, when applied in the early stages of the disease, prolong the life of your patient materially, and in quite a number of cases the ulcerations will heal up, and when your patient dies it is generally by the lung complications, which exist in almost all of these cases

Acute and chronic laryngitis are among our most frequent diseases of the larynx, and are generally concomitant with, or a sequela of, a severe influenza In acute laryngitis, inhalations of hot steam impregnated with comp tr benzoin, eucalyptol and camphor, are very soothing to the inflamed parts, and promote resolution and free expectoration quicker than any other remedy I know In all such cases, remember to keep the secretions open, especially free diaphoresis After the stage of resolution has set in, expectorant treatment accompanied by inhalations of the vapor of terebene, eucalyptol, and camphor will soon get your patient well You must also not forget to treat any existing laryngeal or nasal complications at the same time Counter-irritants are generally condemned, but I have found them act very well in the majority of cases Inhalations of menthol will ease the pain and dysphagia accompanying the acute stages, and should be used through a curved glass inhaler In chronic laryngitis, I have obtained the best results from direct applications of nitrate of silver, menthol in oil, and creosote inhalations The creosote should be used in hot water at a temperature of from 140 to 160 degrees The aphonia which so often accompanies slight attacks of acute or subacute laryngitis, caused by a congested condition of the vocal cords, generally yield nicely to a 10 grain solution of alum or sulpho carbolate of zinc sprayed into the larynx All applications of whatever character must be prolonged, and applied regularly to get good results In most pharyngeal and laryngeal diseases do not depend too much on your patients to carry out your instructions, for all those cases requiring direct applications to the diseased parts *must* be done by yourself If you do not do it yourself, you will very often fail in accomplishing the good results you desire

In the preceding remarks I have confined myself entirely to practical points, gained by personal experience and have only touched upon those which I considered most important, and such as you meet in your daily routine of practice If I have mentioned but one point which may in the future be of some service to you in relieving suffering humanity I shall feel as though I have accomplished *some good*

32 North Second Street

THE PSYCHO-PHYSICAL RELATIONS OF MAN, CONSIDERED FROM THE STANDPOINT OF A PRACTITIONER OF MEDICINE

Read before the Binghamton Academy of Medicine Oc 19 1893

BY JOHN M FARRINGTON, M D
BINGHAMTON N Y

(Continued from page 450)

Excessive fright has often been productive of grave results, and in many instances of sudden death Among the grave diseases induced by fright are mentioned typhus, epilepsy and apoplexy Fear excites especially enuresis, diarrhea and generally produces a relaxation of the sphincters of the mucous passages, causes abortion and predisposes to attacks of contagious and miasmatic disease, while it aggravates every disorder and often renders them fatal We might, if time would permit, refer to many recorded cases of positive and even fatal illness being induced by the imagination only, but one instance or illustration must suffice Lord Stanhope relates the following "An English physician while walking with a friend and conversing with him upon the power of the imagination in its effect upon the health observed a robust and healthy laborer approaching, to prove to his friend the truth of his opinion he accosted the man and inquired after his health, to which he gave satisfactory answers, which seemed to excite much surprise to the physician, and the laborer was gravely and with a sort of affectionate interest told that he was certainly in a state of disease which required great care The laborer immediately returned home and went to bed declaring that he was really ill As soon as the physician learned the ill effects of his experiment he called on the man and apologized, assuring him that he was in perfect health, and that what he had previously said to him was merely to show the influence of the imagination Nothing that he could urge was of any avail The laborer persisted that he was very sick, refused to leave his bed and died in a few days"

But fear has been used with curative effect Various imitative diseases have been arrested by the use of it Boerhave tells us that he once had several patients with epileptiform convulsions from sympathy with a person who fell down before them in an epileptic fit He was puzzled at first how to act, but reflecting that the attacks were produced by a mental impression, he resolved to try the effect of a still stronger impression to check them He ordered, in the hearing of the patients, hot irons to be prepared

and applied to the first person who was seized with a convulsion The consequence was that no more fits occurred afterward Instances are recorded of a prompt cure of gout, asthma and hysteria being accomplished by sudden fright Hildanus relates that a man disguised as a ghost took another laboring under severe gout, carried him down stairs and then left him The terrified invalid quickly found his way up stairs and never afterward was troubled with gout Violent agitation of the mind from indignation, vexation or mortification has a decided effect upon the organism The former inducing at first an excitation of the circulation, while if protracted it has an undermining effect upon all the functions While vexation and mortification induce an interference with the digestive function, nausea and vertigo The effects of melancholy are strikingly exhibited in those who suffer from loneliness or from great misfortune, a general derangement and languid condition of the functions are produced, thus causing a wasting of the tissues But the most obvious effect of a psychical cause is the sudden changing of the color of the hair from dark or gray to white induced by sudden fright or extreme grief "It indicates," says one author, "an extreme sinking in the process of vegetation, because by the perishing of the vascular rète, nothing but the gray or white outer covering remains" Terror will cause the hair to stand on end A state of mind or feeling continually acting upon the body will, usually, in the course of time induce a characteristic change or effect upon the individual's form, gait or expression So marked are these effects we are continually making use of them to aid us in diagnosticating the character and disposition of every person we meet They are signs hung as it were about a man by nature, through the silent yet certain operations of the mind upon the organism

On this influence of the thoughts affecting the features and the character of the expression rest, we believe, the science or art of physiognomy A person who is ever absorbed in mathematical calculations will eventually have traced upon his features an expression indicative of his mind's pursuit One constantly depressed in spirits will wear a "long face" as foreign to mirthfulness as warmth is to an iceberg, his features in time will become so fixed that he will ever exhibit a melancholic air, no matter how much his feelings may change The lineaments of care are indelible We might, did time permit, multiply instances of the same certain results, but it is unnecessary to dwell upon the illustrations to prove that which we every day may witness We are ever making a practical application of the knowledge we have obtained by personal observation, by affixing a character to every face we meet, from the sharp visage of the miser, to the broad benevolent features of the philanthropist, from the bright and cheerful countenance of the contented man to the careworn features of one whose life has been a struggle with misfortune, from the empty expression of the thoughtless to the sedate and thoughtful brow of the philosopher

The passions have a marked effect upon the functions, especially upon the secretions, rendering them greater or less in quantity and of an irritative or perverted character Thus fits of anger in the mother are said to produce a very irritating milk, followed by griping in the infant and green stools, and Dr Van Ammon relates the case of a woman who, while furious from excitement, put her child to the breast and by so doing caused its sudden death, it sank lifeless upon her bosom in a few moments Rage is believed by many physiologists to be capable of generating a most virulent poison in the saliva The effect of anger upon the physical system is most apparent The violent tension of the muscles, and the disordered breathing, disturbing the free circulation of the blood causes it to be thrown back upon the heart and this organ labors with inordinate force to propel it onward Hence a rupture of the heart or large blood vessels sometimes occurs in a fit of anger John Hunter attributed the commencement of his heart disease to a fit of passion Jealousy is thought to act upon the biliary secretion and no doubt does indirectly, by first inducing a disordered condition of the digestive function A variety of colors, present in the different cachexia are attributed to the influence of the passions, thus we have "yellow envy, pale unhappy love and black insatiate hate" A frequent or intense fixation of the attention upon some tragic event described by another may induce the same excitement or agitation of the system as though the tragedy were really witnessed The frequent imitation of the manifestations of certain passions, or the feigning of them may give rise to the real presence of the sensations they were intended to counterfeit Thus actors have died upon the stage, and we once saw an actress brought home from a theatrical rehearsal at which she had swooned, and after her return to consciousness she remained for some time in a high state of nervous excitement and agitation

Perception, as we have heretofore noticed, comes originally from the senses, from the latter as from a starting point or alphabet do the thoughts and fancy branch out, as it were, and incessantly form new data and increased sources of thought, of imagination and perception, which also are subject to corporeal conditions Should the senses be unduly exercised, the organs thus overworked become weakened and injured, and through them the whole system suffers The strain produces an over excitement and perhaps a degree of inflammation of the organs involved, followed by disturbance of the general system Too little employment of the senses, by not assisting the vital process of innervation, occasions a state of general weakness and imbecility Excess of imagination produces the same result as a strain upon the senses only in a higher degree It causes an excitement which is followed by a corresponding depression of all the functions of somatic life Too little exercise of the imagination, like too little use of the senses, induces a low state of the general system and of innervation The same may be said of the redundant or inadequate exercise of the thinking powers Thought has an influence over the vital processes, because of the use it makes of the vital power in its operations and manifestations, its excessive action interferes with the organic functions by abstracting too much of the vital power from the bodily organs, which in consequence of this deprivation are unable to perform properly their functions As thought impedes digestion so as before stated does digestion impede thought This applies with special force to abstract or continued meditation after a meal, or a moderate intensity of thought with a "plenus venter" We have previously alluded to the influence that dyspepsia has upon the mental

condition, we will now notice how the latter may produce the former It is a well-known fact that a large class of dyspeptics are individuals who are giving more or less attention to intellectual pursuits Two reasons have been assigned why such persons are most subject to this disease

1 Because of the sedentary habits which these pursuits or occupations usually involve

2 On account of the well-known sympathy existing between the stomach and the brain

Here, then, is an important point leading to therapeutics or the treatment of the disease in question If dyspepsia has been induced through the operation of mental causes, the mind is the chief channel for the *induction of remedies* The physician here must exercise tact to determine the cause of the functional derangement and then with a nice discrimination select the proper course of procedure to remove it It is unfortunately too common for medical men to pay but little regard to the mental aberrations peculiar to this disease To examine them with attention and, if possible, to afford relief, should be embraced within that philanthropy which ought to be inseparable from our profession The medical adviser should recommend such stimuli to the patient's intellectual and moral powers as seem most demanded to excite a healthy influence upon the organism Profound thought impedes the action of the senses A person may be so buried in his own thoughts as to be, as it were, dead to surrounding stimuli, and utterly unconscious of what is passing about him, thus Archimedes at the storming of Syracuse, remained absorbed in thought, and thus do we observe results often extremely ludicrous from absence of mind, the mind being intent upon something abstract or remote, is not cognizant of corporeal acts Maniacs in their ravings will often inflict ghastly wounds upon themselves without feeling them, the soldier, when comes the "tug of war," is unconscious of his wounds, and the brutal pugilist will bear a multitude of tremendous blows when in the ring but afterwards, when put to bed, becomes sorely conscious of his thumpings and bruises and gives way to groans of agony and exhibits the weakness of a child The power of the prepared mind to resist impressions upon the body is a well-known fact The most courageous man is a coward when taken by surprise, and the bold Indian who laughs at fear, will start like an antelope at a sudden sound

This mental power over bodily pain is also an observed fact, let the mind be prepared for the occurrence and the body is as it were insensible to injury as a marble bust This we have seen in the flagellation of proud-hearted school boys who received the blows from the pedagogue with perfect indifference, or, better still, in the operations at our hospitals, where enfeebled sufferers will sometimes endure a severe operation without a groan The influence of attention upon the bodily organs has been carefully noted by many physicians Dr Brigham in his work on the brain, published in 1840, alluded to this subject He asserts that he has seen tumors, ulcers and eruptive diseases increased and perpetuated by mental attention directed to the diseased part In fact there is scarcely a disease but that may be aggravated by constant anxious thought in reference to it But the important fact to draw from the phenomenon is that not only will mental attention aggravate disease but it will also relieve it Kant was able to forget by the strength of thought, the pain of gout and other diseases, and it is a well-observed fact that calling off the attention of the patient from his disease and fixing it intently upon other matters will have the effect of greatly relieving the suffering from a disordered organism We see frequently, the effects of mental influence in preventing or removing the feeling of fatigue Dr Darwin happily illustrates this influence by reminding us of what we often witness in the child Although heartily tired we have only to give the little fellow our walking stick, he straightway plants it between his legs and rides off as merry as a lark The *modus operandi* of the mind in this case is explained as follows A temporary energy is imparted by the mere effort of the will to the nervous system, and the immediate effect of this is to invigorate the exercise of the respiratory and circulatory systems on the state of which the feeling of fatigue so much depends Many instances are on record where a complete cure has been effected by the influence of mental impressions A humorous anecdote is related of Lord Chief Justice Holt which will illustrate the point under consideration When a young man, Holt was a wild fellow full of jokes and humor On one occasion, with some companions he stopped at an inn in the country where they contracted a debt of such an amount that they were unable to defray it In this dilemma they appealed to Holt to get them out of the scrape Holt observed that the innkeeper's daughter looked remarkably ill and was told by her father that she had the ague Hereupon he gathered several plants and mixed them together with a great deal of ceremony, afterward wrapping them in a piece of parchment upon which he had scrawled certain letters and marks He then hung the ball around the young woman's neck and the ague did not return After this, Holt offered to discharge the bill, but the gratitude of the landlord refused any remuneration and the company left When he became Lord Chief Justice a woman was brought before him accused of being a witch She was the last person tried in England for witchcraft She made no other defense than that she was in possession of a ball which infallibly cured ague The ball was handed to the Judge who found it to be the very one which he had made years before to cure the landlord's daughter and to pay his own bill

I presume every physician present might relate a parallel instance of cases that have come under his own observation, or that of some of his friends, where the mental attention alone upon physical ailments has wrought remarkable results This influence is one of exceeding interest, for by it are we able to explain many phenomena otherwise inexplicable To this is due the apparent success of the legions of charlatans who pose under many different titles such as Faith Curers, Christian Scientists, Spiritualists, etc, and perform such "miraculous cures" They impress the ignorant or superstitious with the fullest and most confident expectation of certain results taking place within their organism, and the power of mental attention thus directed often induces the anticipated result or some approximation to it To our mind this is the true explanation of most of the phenomena produced by animal magnetism The subject must be one of nervous temperament or one who has confidence in the power of the manipulator to induce the mesmeric state or hypnotism,

else the operator fails This power of expectant attention is one that might be used with advantage by physicians in the treatment of disease, and not be left in the hands of the ignorant and the knavish to prey upon and delude those whose ignorance or superstition render them fit victims for this class of mountebanks We all have recognized the effect of expectant attention in some subjects over the action of medicine, so that it is the custom of many physicians to tell the patient what result is expected from the remedy administered We have read of instances where emesis, purgation, diuresis, etc, have been produced by bread pills, the respective patients having been told in advance that the medicine would operate thus The power of expectant attention will induce phenomena without the subject being aware of any voluntary effort to cause their production It is to us a source of satisfaction to know the power that produces the otherwise mysterious phenomena, yet in what manner that influence operates upon the corporeal system we can not tell It is but another of the manifestations of the psycho-physical relations of man, it is a proximate fact, and we can not as yet go further We have previously in this paper referred to the influence of the passions upon the secretions, but there are other mental states that affect the action of the secretory glands, e g, the thought of a luscious fruit or of food may be sufficient to excite an abundant flow of saliva, the maternal affection of the mother for her babe induces a prompt and copious flow of milk at the time of nursing, and excessive feelings of joy or sorrow excite a flow of tears Having thus briefly considered some of the psycho-physical relations, it remains for us to make the same remark which we previously did in reference to the physico-physical relations, to-wit That they do not manifest themselves alike in all individuals They exhibit themselves most in tender and pliable nervous systems Sex, age and education all have an influence The woman, the child and the prematurely developed are the best subjects for their manifestations Premature development and premature education are the causes of a train of both mental and physical diseases As the relations of the mind and the body are affected by too early development of the one and the too early culture of the other, so will they be affected by retarded development of the body and delayed training of the mind Likewise will these relations be disturbed and abnormal where culture of the mind or exercise of the body or both be inordinate or excessive, or if either or both be neglected

Here enter the principles of hygienics, and we are led to appreciate the influence of study and exercise or their opposite, indolence, upon the health of the individual

As before observed we are the subjects of a higher and lower existence—spiritual and animal, two systems of perceptive faculties, one of the body, the other of the mind As we have seen a reciprocal relation exists between them, and our highest happiness in this life will be to so develop the one by exercise and the other by culture as to produce the most perfect state of the intellectual and moral powers that the corporeal frame will permit, without injury to itself, either by inducing disease or shortening life Harmony of the development of the body and mind is essential to harmony of their mutual relations It is a matter of deep regret and humiliating to our civilization to witness the unequal development of these two systems in the inhabitants of our country While some overtax the mind, others overwork the body How sadly the physico-psychical relations are ignored, not only by many parents and teachers in the education of the child, but by adults in their own conduct The body is left to care for itself while the mind is spurred on as long as the poor, pale mortal frame can endure the strain, when death comes to claim the victim of a parent's folly and to lessen the number of the sickly "pale faces" of the nineteenth century Surely we have well earned the title which the Indians gave to our forefathers

"If the mind be overworked by excessive culture, while Nature is engaged in perfecting the body, the demand upon the energies of the system is too great, the one becomes exhausted, while the other is stinted of its fair proportions and dies" We are not, however, one of those who consider that studious habits and intellectual pursuits tend necessarily to injure the health or abbreviate the term of life—that mental labors are ever prosecuted at the expense of the body and must consequently hasten its decay Such a result need not occur if attention be given to the welfare of the corporeal system and the mind be not exerted to an injudicious and excessive extent We have numerous instances of men who have attained great intellectual prominence, and distinguished themselves by the profundity and multiplicity of their mental achievements who by temperate habits and systematic exercise have enjoyed firm health and attained a protracted existence, of which number Wm E Gladstone furnishes us to-day a notable example Yet the inclination of ambitious and intellectual minds is to carry their mental labors to an inordinate and injudicious extent, so that those who possess the highest powers of mind seldom attain great age Sinclair, in his "Code of Health and Longevity," states that in the long list of persons who had lived above a century there is but one individual, Fontanelle (who lived to within a few days of 100 years) at all distinguished for his intellectual powers, while there are above 1,700 others remarkable for little else than the number of their years A well-developed and properly exercised body is especially adapted for the proper performance of the mental functions at the same time a mind duly occupied is essential to the highest enjoyment of health Great advantage accrues from varying the kind of mental exercise so that the mind does not become wearied with any subject and thus render its further pursuit irksome To what extent the mind may be exercised without an ill effect upon the body is a question difficult of solution, and each individual must estimate this point as well as he can from his own experience We have thought very much upon this topic, especially during our student life, and wished that we were able to draw the proper estimate of physical and mental exercise so as to secure harmony of the relations existing between the body and mind and thus obtain the most perfect development of the one, with the highest possible culture of the other We can most feelingly quote Baron Von Swieten (1776) on this subject who says "There is no state on all sides happy, for of all men, those who give themselves up to the study of wisdom might live the most happy if they were not obnoxious to disease from

that very cause Happy are they who can so conduct the healthy exercise of the body together with the improvement of the mind!"

"'Tis the great art of life to manage well
The restless mind"

"At no time," remarks Dr Bell, of Philadelphia, "before or since, has the salutary union between mental and bodily exercise been so fully recognized as in ancient Greece and Rome, where the gymnasiæ and baths were resorted to alike by the philosopher, and the soldier, the youthful aspirant for fame and the staid citizen Often the same person might be seen passing from the instructions of the professed athletæ to the lessons of the sages and orators in the lyceum and the academy, thus while they secured to themselves health and bodily vigor, which should enhance their personal enjoyments and civic usefulness as defenders of the state, they acquired also those accomplishments that give virtue and dignity to the individual, and by reflection to his country and his age However much we may choose to overlook this connection between mental and bodily purity and health, it is not less a portion of natural law, and if true of the one is equally so of the many, and if true in private it is *à futuri*, more valid still in public hygiene When the historian speaks of fermentation among the masses, the poor, the dissolute and the reckless in a city or state, his language is scarcely figurative and he may very appropriately add that this tendency to outbreak and disorder is kept up, if it be not in a great degree produced, by physical deterioration and taint, by impure air causing bad blood and disordered brain, added to filth and bad food continually irritating the nervous system and giving rise to a host of abnormal sensations It is no straining in causation to say that sickness or disorder in the body politic is often the manifestation, as it is the effect, of a neglect of public hygiene So, also, beyond all doubt, have nations been driven into war, with its ever attendant horrors and atrocities, owing to the dyspeptic condition or splenetic humors of princes and ministers of state"

We have already given many illustrations of the influence of the interior life upon the body, and though we may be charged with repetition we can not close our remarks on this influence better than in the words of Newnham "Witness the suffusion of the countenance in blushing, the shrunk features and the pale gooseskin produced by alarm, the chattering of the teeth under fear, the increase of various secretions under mental emotions, as of the tears in sorrow or the bile in anger, the palpitation of the heart under almost every sudden emotion, the short and quickened breathing of expectation, the oppressed and stifled respiration of intense and harrowing emotion, the arrested and almost imperceptible action of breathless anxiety and expectancy, the influence upon the muscles of expression of the countenance, alternately lighted up with joy or worn with anxiety and suffering, and the thousand varied emotions which they are capable of expressing, the plump portliness of the man at ease and the extreme thinness of the victim of deep disappointment, or of any long continued devouring passion, so that to be dried by grief, to be devoured by remorse, to be consumed by sorrow are not only common expressions but literal representations of actual bodily conditions"

We have yet to speak of the psycho-physical relations in the solemn moment of death The phenomena which occur differ with different individuals, depending as they do upon the direct cause of, and the parts or organs which are first affected by death Bichât has stated that death commences from the heart, the lungs or the brain In the first case, the psychical functions would be the latest and slowest in ceasing their manifestations In the second case, the functions of the brain are early impeded and the mind would the more quickly cease to manifest itself, while in the third case the nervous center being primarily affected, a cessation of mental manifestations are the first to occur, consciousness being lost several hours before somatic death occurs Of the senses, observation proves that hearing is the last to expire Again, the mental operations at the hour of death vary in different individuals, seeming often to partake of the quality of those that were most prominent during life and often as has been remarked, "the ruling passion is strong in death"

But however much these relations of body and mind may be modified in the solemn hour of death, here our investigation must cease, the subject of them no longer exists, the relations are sundered, the body is no longer sensible to the excitement of the mind and our eyes are veiled from the spirit's departure, and we are to seek further knowledge of its relations elsewhere than in this life "If no *mortal* lifts the veil we must seek to be immortal"*

We have thus far considered our subject sufficiently, we trust, to prove it not only to be one of profound interest to every thoughtful individual, but of much practical importance to the physician By a knowledge of these relations he may frequently be greatly aided, not only in making a correct diagnosis, but fitted for a more successful treatment of disease From physical signs he may determine psychical causes and from psychical may infer somewhat of somatic Though a single sign may be of little import taken alone, yet if it coincides with others it is often of great value in determining the character of a disease Constitutions differ so materially that we can not mark out an invariable law that will govern all cases, but can only make an approximation in our description of what may be expected from certain psychical or somatic conditions In lively active individuals we may expect a replete and brisk action of the vessels, while in phlegmatic persons the contrary conditions will be present Intense anxiety and melancholy will indicate, with other symptoms, organic disease of the heart or large vessels Thus we might present a long list of psychical or physical signs which are of special interest to the medical practitioner but our limits forbid The physiognomy of the human countenance in sickness is an open book to the medical attendant, to his eye is presented a mirror of many morbid conditions as the countenance changes with the varying stages of the malady, assuming every shade of expression from that indicative of trifling functional derangement, to that which characterizes grave disease The positions that we have taken we do not assume or affirm

* Origin of man and of life—Gen. II 7 'And the Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life and man became a living soul'
The decree of punishment—Gen III, 19 "In the sweat of thy face shalt thou eat bread till thou return unto the ground for out of it wast thou taken for dust thou art and unto dust shalt thou return.
Man s final separation of body and soul—Ecc. XII 7 "Then shall the dust return to the earth as it was and the spirit shall return unto God who gave it

to be immutable laws, they are but general principles founded upon the observation and experience of many writers

Our paper has acquired great length, although we have only taken a very brief survey of this important subject These facts we are to use as points collected for our study, test, and possibly modification, and also as nuclei around which we are to add others as our careful observation or experience shall enable us to do And in our investigations we should remember, as Dr Feuchtersleben has wisely remarked, that, "in all human research and endeavors, it is indispensably necessary carefully to avoid every partial mode of consideration, to hold fast every problem as an enlightening point of instruction, the radii are to be sought and traced everywhere to their origin, but that this process is most especially to be held sacred in our profession, which in every concrete instance presents a countless number of circumstances all equally worthy of attention to every one who has learned, not merely to spell, but to read the book of life" Would time permit we might next consider the changes in the psycho-physical relations which occur in the phenomena of somnambulism and delirium It would also be interesting to sum up the diseases in which these relations specially depart from their normal action Proceeding with our investigations into the pathology of the psycho-physical relations we would next consider the various forms of insanity and amentia, but this is a subject too extensive to allow us to examine at this time As we have found many diseases to be more or less compound, neither purely somatic or purely psychical, but in which both body and mind are more or less involved, we at once appreciate how important a knowledge of the physiology, pathology and therapeutics of the psycho-physical relations are to the physician in the practice of his profession, especially in treating the various psychopathies The psychological physician should possess in a high degree the quality of self-command, and must be able by his personal demeanor to obtain influence over the minds of others He is to be the physician not only, but combine in his person the physician, remedy and vehicle Remedies may be applied through the senses, especially sight and hearing "Light acts as an excitant, twilight as a calmant, darkness according to circumstances acts as both The positive colors act as stimulants, the negative as sedatives"

The mind may be excited by noise, soothed by silence, and cheered by harmony and melody The effect of music is exceedingly pleasant in some cases Bishop Beveridge makes the following observation descriptive of its effects upon him "It calls in my spirit, composes my thoughts, delights my ear, recreates my mind, and so not only fits me for after business, but fills my heart at the present with pure and useful thoughts, so that when the music sounds the sweetest in my ears, truth commonly flows the clearest into my mind, and hence it is that I find my soul is become more harmonious by being accustomed so much to harmony" But an enthusiastic pursuit of the study of music has induced insanity, and it is said that mad musicians are the maddest of the mad

Hope is a most important coefficient to the physician He is often an observer of its guardian power in sustaining the victim during the ravages of dire disease It is a power that every physician should avail himself of, if possible, though it should be used wisely and with a strict adherence to truth, else the confidence that was reposed in him will be lost, and the confidence of the patient in his physician and the remedies employed are as essential to his recovery as hope itself, and even more so, for it can not be inspired if the power be wanting The patient must not be deceived if his illness is to have a fatal termination The rule being, "to speak the truth yet cheer the sufferer" The affections are to be acted upon, the physician should seek to obtain not only the respect but the affections of his patients by bestowing his with a warm and generous heart

In closing my remarks upon the psycho-physical relations of man, I have to regret my inability to do justice to this most momentous subject Yet I trust, however, that my feeble attempt to impress its importance has not been entirely unsuccessful I have tried to illustrate these relations from a medical point of view, and to show that to no one is a true understanding of these relations more valuable and necessary than to the physician, while fortunately to him are presented the most ample opportunities for their study Not a day passes but that he is called to witness illustrations of these reciprocal relations of mind and body No age is exempt from their influence, no profession can fully hide them A fit of indigestion or an aching tooth levels the philosopher with the common herd of mankind All the passions, thoughts, and emotions are at work in a greater or less degree in modifying the physical condition, while every derangement of function or abnormal condition of the bodily organs is exerting an influence upon the mental state

But the interest of the subject does not stop here The fact of man's spiritual nature being involved in all his conditions, whether they be healthy or diseased, gives, as we have before stated, sublimity to our science The accomplished physician has a *medecina mentis* as well as a *medecina corporis* His mission is higher than that of a mere prescriber of the articles of the materia medica To him, alone, does the province belong to treat the entire man The body is not the only object of his care Mind and matter are in man too intimately connected to be studied or treated apart What more need be said of the ennobling influence of the study and practice of medicine? And what is there that gives it such an interest and moral grandeur, unless it be the Psycho-Physical Relation of Man!

CLINICAL HISTORY OF THE CASE OF PRESIDENT JAMES ABRAM GARFIELD

BY ROBERT REYBURN, A M, M D

PROFESSOR OF PHYSIOLOGY AND CLINICAL SURGERY MEDICAL DEPARTMENT HOWARD UNIVERSITY, WASHINGTON, D C, AND ONE OF THE ATTENDING SURGEONS IN THE CASE OF PRESIDENT GARFIELD

(*Continued from page 417*)

III

July 24, 8 A M The President's skin is drenched with a profuse perspiration His skin is cool, with a somewhat anxious expression of countenance An examination of the wound was made by the consulting and attending surgeons, and a small pus sac was found about three inches from the external wound (in a downward direction) After consultation it was deemed advisable to make a counter opening three inches below the wound for the purpose of drainage

The skin was sprayed with sulphuric ether to diminish the sensibility of the parts, and the opening was made by Dr Agnew assisted by Dr Hamilton A large drainage tube was tied in communicating with both openings The wound was then dressed, and he was given one ounce of Liebig's extract of beef, and afterwards three ounces of milk and one teaspoonful of rum

July 24, 12 M The President feels much more comfortable since the operation His skin is much more natural in hue He is still sweating profusely but there is no evidence of rigors He has vomited once slightly this morning, but has taken and retained some nourishment

July 24, 12 M Temperature 99 8, pulse 118, respirations 24 July 24, 7 P M Temperature 99 2, pulse 104, respirations 23 July 24, 5 P M The President is much more comfortable to-day than yesterday He has slept a good deal at intervals during the day, and has retained all the beef essence given To-day Professors Bell and Newcomb came to the President's room with Mr Tainter and demonstrated the use of the induction balance for discovering bullets in the human body Professor Agnew returned to Philadelphia in the 5 40 P M train, but Professor Hamilton remained over during the night in Washington July 24, 6 P M The wound was dressed, and thoroughly washed out with a weak solution of carbolic acid (one-fourth of 1 per cent) He received a hypodermatic injection of one eighth of a grain of sulphate of morphia at 7 P M, and slept tolerably well during the early part of the night He vomited once at about 10 30 P M He took small quantities of beef juice and milk during the night At 3 30 A M he had a profuse sweat He was rubbed off with a solution of alum and then with alcohol

July 25, 8 A M The President seems quite cheerful this morning, and takes his liquid food freely and with relish He passed a comfortable night, and has had no rigor since yesterday July 25, 8 39 A M Temperature 98 4, pulse 96, respirations 18 July 25, 12 M Temperature 98 4, pulse 106, respirations 20 July 25, 7 P M Temperature 101 8, pulse 110, respirations 24 At 12 M he took six grains of quinia (bisulphate) and at 3 30 P M he complained of feeling cold Bottles of hot water were placed at his feet, and he was well rubbed He vomited once, and after the vomiting he had a profuse sweat He was quiet but did not take much nourishment during the day with the exception of beef essence He had a hypodermatic injection of one eighth of a grain of morphia at 7 P M He slept for an hour or two, and at 11 30 P M had another slight rigor He complained of chilliness which was followed by fever and sweat during the night Professor Agnew arrived at 12 (midnight) The President was somewhat restless during the night, and the fever which had subsided during the evening rose again about midnight, and continued until 3 A M after which it again subsided

July 26, 8 30 A M Temperature 98 4, pulse 102, respirations 18 July 26, 12 M Temperature 98 4, pulse 106, respirations 19 July 26, 7 P M Temperature 100 7, pulse 104, respirations 22 July 26, 8 A M The President is quiet and does not complain of pain

July 26, 8 A M The wound was dressed, and Dr Agnew enlarged the opening over the rib, and extracted therefrom a fragment of bone which had been driven in by the bullet, and was lying loose in the inner track of the wound Some fragments of muscle and connective tissue were also removed The largest piece of bone removed was about an inch in length There were also small particles of bone taken out The wound was well irrigated with the quarter per cent solution of carbolic acid, and two drainage tubes were fastened in the lower wound, one entering the cavity, and one draining the lower opening of the wound The President bore the operation remarkably well, and in fact his condition seemed much more comfortable after the dressing and operation than it was before

July 26, 12 M He took six grains of bisulphate of quinia During the afternoon he had several good naps, and took liquid nourishment quite freely At 3 39 P M the President had a slight sweat 5 30 P M He was given six grains of bisulphate of quinia 11 P M The President had his hypodermatic injection of one-quarter of a grain of sulphate of morphia at 7 30 P M, after a short time he went to sleep and slept until 11 P M when he awoke, and after a little while he went to sleep again, and slept soundly until 5 A M

July 27, 7 30 A M This morning he took beef essence, and four ounces of koumiss July 27, 8 A M Temperature 98 4, pulse 94, respirations 18 July 27, 12 30 P M Temperature 98 4, pulse 90, respirations 18 July 27, 7 P M Temperature 98 8, pulse 96, respirations 20

July 27, 8 30 A M The President's wound was dressed and looked well There were no rigors nor febrile rise of temperature during the day He took his liquid nourishment freely and without any apparent disorder of the stomach He received his hypodermatic injection of one-fourth of a grain of sulphate of morphia at 7 40 P M and slept well during the night, sleeping at one time three hours without interruption

July 28, 8 A M The President was very cheerful this morning, and seemed to feel comfortable July 28, 8 A M Temperature 98 4, pulse 92, respirations 18 July 28, 12 30 P M Temperature 98 5, pulse 94, respirations 18 July 28, 7 P M Temperature 100 5, pulse 104, respirations 20

Professor Hamilton was present at the morning dressing of the wound During the morning the patient took bouillon, beef juice, milk, with an egg beaten up in it, and one teaspoonful of rum At 10 18 A M he took six grains of bisulphate of quinia During the morning the President's room was thoroughly aired and cleaned, and all the carpets and upholstered furniture were removed He took a good deal of liquid food to-day, and had no febrile rise until 4 P M when he complained of feeling a little feverish The wound was again dressed at 6 P M and the drainage tube being found to be obstructed was removed, and a larger tube inserted At 7 40 P M he received a hypodermatic injection of one-eighth of a grain of sulphate of morphia, and went to sleep at 9 P M At 10 30 P.M he complained of a sharp pain over the region of the bladder, this was relieved by hot fomentations and he went to sleep again at 11 30 P M At 11 30 P M his temperature was 99 8, pulse 98, respirations 19

July 29, 7 A M The President slept well, and awoke feeling refreshed The wound was dressed at 8 15 A M and was found to be in an excellent condition He is still taking liquid food only, consisting of milk and egg with a little rum alternating with

koumiss and beef juice July 29, 8 30 A M Temperature 98 4, pulse 92, respirations 18 July 29, 12, 30 P M Temperature 98 4, pulse 98, respirations 19 July 29, 7 P M Temperature 100, pulse 98, respirations 20

July 29, 8 30 A M Immediately after the evening dressing yesterday the President's afternoon fever began to subside He bore the dressing of his wound well, and exhibited very little fatigue after its completion 7 P M The President has been cheerful during the day His wound was dressed the second time at 1 30 P M The febrile rise came on later and was not so marked as yesterday He received his usual hypodermatic injection of one-eighth of a grain of sulphate of morphia about 8 P M and slept well during the night taking liquid nourishment at 1, 3 and 6 A M

July 30 8 30 A M The slight febrile rise of yesterday afternoon had subsided by midnight, and this morning his temperature is again normal July 30, 8 30 A M Temperature 98 5, pulse 92, respirations 18 July 30, 1 P M Temperature 98 5, pulse 98, respirations 20 July 30, 7 P M Temperature 100 2, pulse 104, respirations 20

July 30, 8 30 A M The President slept well until 8 40 A M His wound was then dressed, and found to be discharging freely At 9 10 A M he took some rare beefsteak and scraped beef for breakfast, following this with six ounces of koumiss At 10 A M he took six grains of bisulphate of quinia During the day he received a good share of liquid food, had several naps, and expressed himself as feeling quite comfortable A head rest elevating the upper portion of his body was placed under the mattress of his bed, by means of which his head and shoulders have been somewhat raised, and he expressed himself as much pleased by the change of position The afternoon rise of temperature was moderate and did not commence until 5 P M Professor Agnew arrived to-day, and was present at the evening dressing along with Professor Hamilton (Professor Hamilton has remained continuously on duty with the attending surgeons since July 27) A small drainage tube was passed farther into the cavity of the wound than heretofore, and the wound was thoroughly washed out with the quarter per cent solution of carbolic acid He received a hypodermatic injection of one-twelfth of a grain of sulphate of morphia, and went to sleep at 8 15 P M

July 31, 8 39 A M The President slept well during the night, and expressed a desire for solid food After his wound was dressed he took a lamb chop for breakfast Professor Hamilton returned to New York this morning while Professor Agnew remained in Washington The afternoon fever of yesterday subsided earlier than the night before, and had quite disappeared by 10 P M

July 31, 8 30 A M Temperature 98 4, pulse 94, respirations 19 July 31, 12 30 P M Temperature 98 5, pulse 94, respirations 19 July 31, 7 P M Temperature 99, pulse 104, respirations 20

The President bore the morning dressing of his wound well He took and retained an ample supply of nourishment to-day, and seems to improve in his general condition An enema was given him this afternoon The wound looks well, and the secretion from it is quite abundant The wound was dressed the second time at 6 P M At 7 30 P M he received his hypodermatic injection of one-twelfth of a grain of sulphate of morphia, and slept well during the night.

August 1, 8 A M The President awoke quite refreshed this morning and said he had spent the best night since his injury His wound was dressed at 8 35 A M and quite a free flow of pus came from it After the dressing Professor A G Bell and Mr. Tainter tried for the second time the induction balance, for the purpose of endeavoring to locate the bullet in the President's body This was an apparatus composed of a series of induction coils, so arranged that on being brought near a metallic body the electric balance would be disturbed, and a sound produced Both Professor Bell and Mr Tainter from these experiments located the ball in a space about two inches in diameter, somewhat to the right, and four and a half inches below the umbilicus As will be seen hereafter this localization of the bullet was an error, and aided in confirming the erroneous diagnosis, which had been previously made by the consulting and attending surgeons as to the location of the bullet The pus from the wound (though it was thoroughly washed out twice, and sometimes three times a day, and allowed free exit by means of drainage tubes) gradually formed a sinus or false passage in a downward direction from the wound The transverse wound through the body of the first lumbar vertebra, from its irregular and rough character entirely prevented the passage of any probe in that direction, hence from all the means of information at our disposal, we were led to the belief that the bullet was located in the right side of the abdomen below the point of entrance After the testing of the induction balance the President took some beefsteak, toast and gravy and a cup of coffee At 11 A M he was given six grains of bisulphate of quinia, and this dose was repeated at 4 30 P M During the day the President seemed somewhat tired, and took several naps He was given the usual amount of liquid food including koumiss He complained during the afternoon that the koumiss had seemed to disagree with his stomach Food was withheld from him for a short time with the effect of relieving him

August 1, 8 30 A M After the slight rise of temperature yesterday afternoon it became normal early in the evening, and so continued during the greater part of the day August 1, 8 30 A M Temperature 984, pulse 94, respirations 18 August 1, 12 30 P M Temperature 98 4, pulse 100, respirations 19 August 1, 7 P M Temperature 99 5, pulse 104, respirations 20 August 1, 7 45 P M He received one-eighth of a grain of sulphate of morphia hypodermatically, and slept well during the night

August 2, A M The President slept well until 8 A M, when his wound was dressed as usual A new soft long catheter (No 8) was passed into the opening of the eleventh rib, and passed downward into the abdominal cavity between three and one-half and four inches, and allowed to remain Another drainage tube was put into the external lower wound (the one made by the incision) and both were kept in place by strips of adhesive plaster Discharge of pus from wound was free

August 2, 8 30 A M Temperature 98 4, pulse 94, respirations 18 August 2, 12 30 P M Temperature 98 4, pulse 99, respirations 19 August 8, 7 P M Temperature 100, pulse 104, respirations 20

August 2 The President had an enema at 2 30 P M The wound was dressed at 6 P M and he complained of darting pains during the evening radiat-

ing from wound The discharge from the wound was quite profuse He had at 7 45 P M one eighth of a grain of sulphate of morphia hypodermatically, and slept well during the night

August 3, 8 A M The President passed a comfortable night and this morning the long, soft rubber tube was removed from the wound (it seeming to cause irritation), and a short, wide drainage tube was inserted in its place Dilute solution of permanganate of potash was used to wash out the wound instead of the dilute solution of carbolic acid The strength of the solution of permanganate used was eight grains to two pints of water at the temperature of 100 F Professor Agnew (who had been on duty with the attending surgeons since July 30) returned to Philadelphia at 9 30 A M At 5 30 A M the President took six ounces of koumiss, at 7 30 four ounces of bouillon and two teaspoonfuls of beef juice, and at 9 A M six ounces of milk and two teaspoonfuls of rum He went to sleep at 9 45 A M and slept until 10 45 A M when he took six grains of bisulphate of quinia, and the same dose at 5 40 P M At 11 30 A M he breakfasted and took a little steak, toast and potato He passed a very comfortable day The discharge from the wound was profuse and laudable in character During the afternoon he had scarcely any pain, and his temperature remained normal until the evening, when it was one degree above During the day he took a good supply of liquid food

August 3, 8 30 A M Temperature 98 4, pulse 96, respirations 18 August 3, 12 39 P M Temperature 98 4, pulse 100, respirations 19 August 3, 7 P M Temperature 99 4, pulse 102, respirations 19

He received his hypodermatic injection of one-sixteenth of a grain of sulphate of morphia at 8 P M and went to sleep at 9 P M He slept well during the night, waking at 3 A M for a short time He then slept until 8 A.M of August 4 Professor Hamilton arrived last night (August 3) and will remain until Professor Agnew returns August 4 Wound was dressed at 8 A.M The drainage tube was removed and a smaller tube inserted Diet the same as yesterday 12 30 P M He was given six grains of bisulphate of quinia At 12 M Professor Hamilton made a careful examination of the President, and found a small point of induration, one and a quarter inches to the left of anterior superior spinous of right ilium, and about the center of a line drawn from one anterior superior spinous process to the other The President had an enema at 4 P M and at 6 P M he took six grains of bisulphate of quinia

August 4, 8 30 A.M Temperature 98 4, pulse 90, respirations 18 August 4, 7 P M Temperature 100 2, pulse 102, respirations 19

The President passed a good day without drawbacks of any kind He took his nourishment well, and has shown little fatigue after his dressings, and changes of position The wound looks well The President took a fair amount of liquid food during the day, and went to sleep at 9 P M and slept well during the night He received no morphia at bedtime to-night

August 5, 8 30 A M The President slept naturally during the greater part of the night, though he has taken no morphia for the past twenty-four hours His improved condition warranted several days ago a diminution in the quantity of morphia administered hypodermatically at bedtime, and it was reduced at first to one-twelfth, and then to one sixteenth of a grain in the twenty-four hours without any unpleasant results, and finally has been altogether dispensed with Yesterday and to day only two bulletins have been issued, in place of three as heretofore August 5, 8 30 A M Temperature 98 4, pulse 88, respirations 18 August 5, 7 P M Temperature 100 4, pulse 102, respirations 19 August 5, 6 A M He took seven ounces of koumiss At 9 10 A M seven ounces of milk with two teaspoonfuls of rum At 11 40 A M he breakfasted on toast, beefsteak and potatoes in small quantities At 9 30 A M. he was given six grains of bisulphate of quinia At 12 M he took four ounces of koumiss At 1 P M he took six ounces of milk and two teaspoonfuls of rum At 3 10 P M he had three and a half ounces of chicken jelly At 5 P M he took beef juice and bouillon, and at 7 30 P M he took six ounces of milk and two teaspoonfuls of rum Wound was dressed at 6 P M and the discharge was abundant No hypodermatic injection of morphia was given this evening The President did not get to sleep until after 9 P M and awoke at 11 15 P M for a short time and then slept through the night until 6 30 A M August 6

August 6, 3 A M The President took three ounces of Valentine beef juice, and two and a half ounces of bouillon At 7 A M he took six ounces of milk with two teaspoonfuls of rum 8 A M Dressed the wound as usual The cavity of the wound was measured and found to contain two ounces of fluid To-day it was deemed best to suspend the administration of the bisulphate of quinia, and to give instead two teaspoonfuls of compound tincture of gentian three times a day Claret was also directed to be given as a beverage He took during the morning four ounces of the claret Breakfast consisted of a small quantity of steak, toast and potatoes

August 6, 8 30 A M Temperature 98 4, pulse 92 respirations 18 August 6, 12 30 P M Temperature 98 5, pulse 100, respirations 19

The President passed a comfortable morning but towards the afternoon he complained very much of exhaustion from the excessive heat The external temperature was such that it was found impossible to keep the temperature of his room below 90 degrees F without closing the doors and windows, which was not thought prudent During the day the President took a good deal of liquid, but scarcely any solid food Towards the afternoon his febrile symptoms seemed to become more aggravated, and he was greatly exhausted by the evening dressing No quinia was given to-day, and his tongue seemed to clear off At 8 P M Professor Agnew arrived At 10 P M the President took seven ounces of milk with three teaspoonfuls of rum He soon afterwards went to sleep, and slept the greater part of the night

August 7 From 1 to 5 A.M the President had a slight febrile rise which passed off by 8 A M At that hour his temperature was 98 7 At 6 A M he took six ounces of koumiss, at 8 15 six ounces of milk, and two teaspoonfuls of rum At 11 A M he breakfasted on a little steak, toast and potatoes At 11 15 A M he had four ounces of koumiss At 1 P M he had seven ounces of milk At 3 20 P M he took four ounces of claret The President complained so much of the compound tincture of gentian that it was stopped, and six grains of bisulphate of quinia given instead The President complained to-day of slight chilliness, and of pain in the region of the wound and in the limbs

August 7, 8 30 A M Temperature 98 7, pulse 96, respirations 18 August 7, 12 M Temperature 100, pulse 104, respirations 20 August 7, 7 P M Temperature 101 2, pulse 104, respirations 20

August 7 The President was fairly comfortable during the day, although his temperature began to rise earlier than yesterday, and rose almost as high At the morning dressing it was found that the entrance of wound through the eleventh rib was apparently obstructed by the drainage tube with accumulation of pus in the cavity of the wound At 6 P M the wound was dressed as usual The drainage tube was temporarily removed, and the President was placed on his right side for the purpose of promoting drainage from the wound, for about an hour during the afternoon and evening The President passed a quiet night, and slept well without the use of any anodyne The rise of temperature of the afternoon subsided during the evening and did not recur at any time in the night

(To be continued)

Report of the Committee on Revision of Constitution, By-Laws and Code of Ethics of the American Medical Association, with Amendments

To the President and Members of the American Medical Association

Gentlemen Your Committee, to which was committed the task of studying the Constitution and By-Laws of the AMERICAN MEDICAL ASSOCIATION, with a view of determining whether they could be changed in any manner so as better to promote the development of the Association, and better to advance the interests which it represents, have had the same under most careful consideration, and submit the following, which has already been published in the JOURNAL of the Association and other medical periodicals

AMERICAN MEDICAL ASSOCIATION

CONSTITUTION AND BY-LAWS

HISTORY

In May, 1846, a medical convention was held in the city of New York to consider measures for the elevation of the medical profession in all its constituent elements, and for the promotion of its organic unity After much discussion this convention declared that a National organization of every State and interest was demanded Committees were appointed to draft a Constitution, By-Laws and a Code of Ethics, and to report at a meeting to be held the following year Accordingly, in May, 1847, representatives of the profession of the United States met in Philadelphia, heard and discussed reports of the committees, organized under the name of the AMERICAN MEDICAL ASSOCIATION, and adopted a Code of Ethics, a Constitution and By-laws, which, with slight alterations, have continued to direct the organized movements of the profession until the present time In compliance with the instruction of the Association in June, 1892, the following Constitution and By-Laws, are formulated for the purpose of promoting the best activity of a general medical organization of the profession in North America

CONSTITUTION

Name—This organization shall be known as THE AMERICAN MEDICAL ASSOCIATION

MEMBERS

Members—Membership shall be limited to the members of the several affiliated State medical societies recognized thereby or represented therein As membership in these societies is open to all reputable practitioners in each State, the membership in the AMERICAN MEDICAL ASSOCIATION is open to all reputable physicians in North America

All persons now members of the Association shall continue such so long as they remain in good standing in their State society, and pay their annual dues If they desire to participate in any annual meeting, they shall present to the Committee of Arrangements of said meeting a certificate from the officers of their State or local society to the effect that their standing is good, and one from the Treasurer of the Association showing that all dues are fully paid To all presenting such certificates, the Committee of Arrangements shall issue the credentials necessary for active participation in the annual meeting

All members of recognized State or local medical societies may become members of the Association by presenting to the Committee of Arrangements at any annual meeting a certificate from the officers of their society showing that they are in good standing therein, and a certificate from the Treasurer of this Association showing that they have paid their annual dues

All members of the recognized State or local medical societies who are unable to attend the annual meeting may become members of the Association by sending to its Treasurer, at any time, a certificate from the officers of their society of their good standing, and remitting the annual dues

All members who have fulfilled these two conditions shall have equal rights and equal responsibilities in the Association, and shall regularly receive the Association JOURNAL

All State medical societies, with their constituent local societies, shall be recognized by the AMERICAN MEDICAL ASSOCIATION if they accept its Code of Ethics

Members of Canadian and Mexican medical societies shall be admitted to membership upon the same terms as those in the United States The regular graduates of such schools and colleges of dentistry as require of their students a standard of general education and a term of professional study equal to those of the best class of medical colleges in this country, and embrace in their curriculum all the fundamental branches of medicine, differing chiefly by submitting practical and clinical instruction in oral and dental surgery in place of practical and clinical instruction in general medicine and surgery, shall be recognized as members of the regular profession, and shall be eligible to membership upon the same terms as other members

No persons shall be permitted to take part in any annual meeting until they have completed the conditions of membership at that meeting, and can exhibit certificates to this effect from the Committee of Arrangements But suitable persons may be introduced as guests either at the general session or the Section sessions, and be invited to engage in the scientific and social exercises of the meeting without taking part in the transaction of business

MEETINGS

Meetings—The regular meetings shall be held an-

nually at such time and place as may be advised by the Business Committee and ordered by the Association The details of these meetings are stated in the By-Laws

OFFICERS

Officers—The officers of this Association shall be a President, four Vice-Presidents, one Secretary, one Assistant Secretary, a Treasurer and a Librarian These officers shall hold office during one year or until their successors are elected, and shall enter upon their duties immediately after election

The President shall preside at the meetings, preserve order and decorum in debate, giving a casting vote when necessary, and perform all the other duties that custom and parliamentary usage may require At the opening session he shall deliver an address to the general meeting, not to exceed thirty minutes in length

The Vice-Presidents may be called upon to assist the President in the performance of his duties, and during his absence, or at the request of the President, one of them shall officiate in his place

The Secretary shall record the minutes of the general sessions and authenticate the proceedings, give due notice of the time and place of the next annual meeting, notify all members of committees of their appointment and the duties assigned to them, hold correspondence with other organized medical societies, both domestic and foreign, and carefully preserve the archives and unpublished transactions of the Association

For his personal expenses in attending the annual meetings the Secretary shall draw upon the Treasurer of the Association

The Assistant Secretary shall aid in recording and authenticating the proceedings of the Association, serve as a member of the Committee of Arrangements, and perform all the duties of the Secretary temporarily, whenever that office shall be vacant by death, resignation or removal

The Treasurer shall have the charge and management of the funds of the Association He shall give the Board of Trustees bonds for the safe keeping and proper use and disposal of his trust Through the same Board he shall present his accounts, duly authenticated, at each regular meeting He shall each month furnish the President of the Board of Trustees with a statement of accounts for the guidance of the Board in its expenditures For his personal expenses in attending the annual meetings, he shall draw upon the treasury through the President of the Board of Trustees

The Librarian shall receive and preserve all property in books, pamphlets, journals and manuscripts presented to or acquired by the Association, record their titles in a book prepared for this purpose, and acknowledge the receipt of the same He shall deposit these documents in such place and manner as the Association may direct, after advising with the Board of Trustees

STANDING COMMITTEES

The Committee of Arrangements shall be composed of at least seven members, of whom the Assistant Secretary shall be one, all residing in the place at which the Association is to hold its next annual meeting It shall provide suitable accommodations for the meeting, shall verify and report upon the credentials of membership, shall issue credentials of membership to such as fulfill the conditions shall publish the rules governing the reading and discussion of papers and the order to be observed in the business of the general and sectional meetings, shall receive and announce all papers communicated, and, with the several Section Secretaries determine the order in which the papers shall be read and discussed, shall prepare a list of members present on a separate roll for convenience in calling the ayes and nays, when these are demanded, and shall cause all members to register their names, residences and temporary addresses during the annual meeting, and the name of the Section in which they will severally vote for Section officers The expenses of a hall for the general meeting, of rooms for the Sections, and of cards of membership, shall be met by the Association Should the Committee incur other expenses, it must meet them from its own resources

This Committee shall be nominated by the Business Committee, and elected by the Association

The Board of Trustees shall consist of nine members, three of whom shall be elected annually on nomination of the Business Committee, and serve for three years This Board shall manage all matters relating to finance and publication It must provide for and superintend the publication and distribution of all such proceedings of the Association as may be ordered to be published, in such manner as the Association may direct In doing this it shall have authority to appoint an editor and such assistants as may be necessary, and to determine their salaries It shall procure and control such materials as may be necessary for the performing of the duties assigned it To the Board or its representatives must be delivered, during the annual meeting, or as soon thereafter as is possible, by the Secretary of the Association and by the Section Secretaries or Executive Committees, all records of meetings, papers or discussions, and such other documents as were ordered published by the Association

All money received by the Board of Trustees or its agents, resulting from the discharge of the duties assigned them, must be paid to the Treasurer of the Association, and all orders for disbursements of money, in any way connected with the work of publication, must be indorsed by the President of the Board of Trustees It shall further be the duty of the Board of Trustees to hold the official bond of the Treasurer for the faithful execution of his office, to annually audit and authenticate his accounts, and present a statement of the same to the Association This report must specify the character and cost of all publications of the Association during the year, the number of copies still on hand, and the amount of all other property belonging to the Association, under its control, with such suggestions as it may deem necessary It shall yearly publish a list of members, their addresses in full, year of admission, the Constitution and By-Laws and Code of Ethics, and such other information as may be deemed useful, for distribution to the members at each meeting

At the opening of each volume it shall publish a disclaimer by the Association for any responsibility for opinions expressed in the volume

To this Board must be referred all propositions for the appropriation of money, to be considered and reported upon before the final action on the same by the Association

The General Business Committee shall be com-

posed of the several Section Executive Committees, selected as hereafter described It shall hold daily meetings during the sessions of the Association, and such other meetings as may be deemed necessary for the performance of its duties All matters of business not provided for by the Committee of Arrangements, the Board of Trustees, the Judicial Council and Special Committees, shall be referred to it without debate, for consideration and report to the Association In general, this Business Committee shall give especial attention to the interests of the Association as a whole, and through these interests shall seek the development of the Sections, it shall consider all matters of business referred to it by the Association, and report upon them at the earliest possible moment, when the Association may accept or reject said report, as it may deem best

It shall be the duty of this Committee to seek the removal of such obstacles as interfere with the cordial cooperation in the Association of all competent, honest practitioners of rational medicine throughout this continent, and to promote every means by which cooperation shall be effected and maintained

The General Business Committee shall make and present the nominations for officers of the Association and its Standing Committees, and recommend the time and place of the ensuing meeting It shall appoint its own officers, and adopt rules for the orderly performance of its duties Finally, it is expected that it will perform all its duties in the interests of the advancement of scientific medicine

The Judicial Council shall consist of twenty-one members, whose duty it shall be to take cognizance of and decide all questions of an ethical or judicial character which may arise in connection with the Association, and the Association will accept such decision as final

Of the twenty-one members first appointed, the first seven named upon the list shall hold office one year, and the second seven two years With these exceptions, the term of office of the members of the Judicial Council shall be three years, seven being nominated by the Business Committee yearly, and elected by the Association The Council shall organize by choosing a President and Secretary, and shall keep a permanent record of its proceedings The decisions of said Council shall be final upon all ethical questions referred to it by the Association, and must be accepted without debate Such decisions shall be reported to the Association as soon as practicable

All questions of a personal character, including complaints and protests, and all questions on the ethical standing of medical societies shall be referred at once, when presented to the Association, to the Judicial Council, and without debate

INCOME AND EXPENSES

The income of the Association shall be derived from subscriptions to its journal and advertisements therein, from specific publications and voluntary contributions for specific objects

Its funds may be appropriated for the expenses of halls, for general sessions and Section meetings, and for cards of membership, and such other expenses of the annual meeting as are essential for the conduct of the routine work, for meeting the necessary personal expenses of the Secretary and Treasurer while attending the annual meetings and in conducting the necessary correspondence, for publications, for enabling standing committees to fulfill their respective duties and conduct their correspondence, for the encouragement of scientific investigation by prizes, and for defraying the expenses of scientific investigation under the instruction of the Association, where such investigation has been accompanied with an order upon the Treasurer to supply the funds necessary for carrying it into effect

AMENDMENT

No amendment or alteration shall be made in any of these rules except at an annual meeting next subsequent to that at which such amendment or alteration may have been proposed, and then only by the voice of three-fourths of all the members present Provided, however, that when an amendment is properly under consideration, and an amendment thereto is offered germane to the subject, it shall be in order, and if adopted, shall have the same standing and force as if proposed at the preceding meeting of the Association

BY-LAWS

1 Order of Business—The order of business at the annual meetings of the AMERICAN MEDICAL ASSOCIATION shall be subject to the vote of three fourths of all the members in attendance Until thus altered, except when suspended, it shall be as follows

1 Calling the meeting to order by the President
2 The report of the Committee of Arrangements on the credentials of members, after the latter have registered their names and addresses, and on such other matters as it desires to present to the Association
3 The reception of guests of the Association
4 The annual address of the President
5 The reception of reports from all special committees
6 The reading and consideration of reports of standing committees, the Board of Trustees, Business Committee and Judicial Council
7 New business and instructions to standing committees
8 The report of the Business Committee and the election of officers of the Association, the selection of next place of meeting
9 Reports from the Executive Committees of the Sections
10 Reading of the minutes by the Secretary
11 Unfinished and miscellaneous business
12 Adjournment

MEETINGS

The Annual Meetings of the AMERICAN MEDICAL ASSOCIATION shall be held in May if the place be in the South, and in June if the place be in the North The day of opening of the general sessions shall be the first Tuesday after the first Monday of the month selected The hour of opening on the first day shall be 10 A M, and on the following days 4 30 P M

SECTIONS

The several Sections shall hold their first meeting at 1 30 P M, on the first day, and at 9 A M and 1 30 P M thereafter daily

The several Sections are as follows

1 Practical Medicine and Physiology
2 Obstetrics and Diseases of Women
3 Surgery and Anatomy
4 Orthopedic Surgery

5 State Medicine
6 Ophthalmology
7 Diseases of Children
8 Dental and Oral Surgery
9 Medical Jurisprudence and Neurology
10 Dermatology and Syphilis
11 Laryngology and Otology
12 Materia Medica and Pharmacy

Officers of Sections—The officers of each Section shall consist of a Chairman, Secretary and Executive Committee The Chairman and Secretary shall be elected annually immediately after the Section is called to order on the afternoon of the second day During the session of the first day, the Chairman shall appoint a Nominating Committee, consisting, if practicable, of ex-chairmen of the Section, to report at the opening of the afternoon session of the second day Election shall be by ballot

The Executive Committee of each Section shall, when first appointed, consist of three members from among those who have been in attendance at the sessions of the Section for at least two years, to serve for one, two and three years respectively, and thereafter the retiring Chairman of the Section shall take the place upon the committee of the retiring member It shall be the duty of the Executive Committee, in conjunction with the Chairman and Secretary, to give special attention to the interests of their own Section Thus they shall secure the annual republication from the JOURNAL of the work of the Section, its papers and discussions, list of officers, lists of all members of the Section, with their addresses, and rules adopted by the Section for the conduct of its work, securing from the Section the funds needful for the performance of this purpose They shall carefully edit all publications of the Section, and secure a creditable mechanical execution of the same They shall also take such measures as in their judgment will secure the cordial cooperation of all reputable workers in their special fields in North America

The several Executive Committees of the Sections shall meet together and form a General Business Committee of the Association, with powers and duties described under the head of the General Business Committee

The Chairman of each Section, in addition to his duties as a presiding officer and a member of the Executive Committee, shall read a short address at the opening of the session on the first day In conjunction with the Secretary, he shall secure from members papers to be read, and arrange for the discussion of the same This order of Section work he shall communicate to the Chairman of the Committee of Arrangements at least one month before the annual meeting

No paper read before the Sections shall occupy more than twenty minutes If it be longer, the writer should make such an abstract as will bring it within the limit, and present it for discussion No person shall discuss any paper more than once, or speak longer than fifteen minutes without unanimous consent

No paper shall be read before any Section that is not in such condition as to pass at once from the reader's hands to the Executive Committee of the Section Within thirty days, said Committee must forward the entire work of the Section to the Board of Trustees, with such recommendations as it deems proper But no paper shall thus be sent by an Executive Committee that does not fall under one of the following heads

1 Such as may contain and establish new facts, new modes of practice or new principles of real value

2 Such as may contain the results of well-devised original experimental research

3 Such as present so complete a review of the facts on any particular subject as to enable the writer to deduce therefrom legitimate conclusions of importance

Other papers containing material of more or less value shall be returned to their authors, to be published as they may desire, with the statement that they were read before said Section of the AMERICAN MEDICAL ASSOCIATION

In general it is expected that each Executive Committee will make every effort to secure for its special Section, papers and discussions which will fairly represent the active workers in their department of medicine, and to promote cordial good will among the several workers therein

PUBLICATION OF PAPERS AND REPORTS

All papers and reports must be so prepared as to require no material alteration or addition at the hands of authors All Section work must be in the hands of the Trustees within thirty days after the annual meeting Proofs will be sent authors, but they should be returned at the earliest possible moment, and unless returned within two weeks, the paper may be omitted from the JOURNAL Every paper requiring it shall be illustrated at the expense of the Association, should it accept the same for publication Every paper accepted is understood to be contributed exclusively to the Association JOURNAL, though brief extracts of the same may be published elsewhere In case of an article that is of especial value, the result of expensive research or experimentation, the Trustees, at their discretion, may compensate the writer in accord with the usual price of such work

The Board of Trustees has the power to reject any paper referred to it, unless especially instructed to the contrary by the Association

DUES

Each member of the Association shall pay the annual subscription to the JOURNAL of five dollars before receiving from the Committee of Arrangements the membership ticket to the annual meeting The evidence of this shall be the Treasurer's receipt for the five dollars Any member failing for one year to pay this subscription shall be dropped from the rolls

DELEGATES

The President of the AMERICAN MEDICAL ASSOCIATION is authorized to appoint members, desiring such appointment, as delegates to the several medical and scientific bodies that are in sympathy with the Association

DUTIES OF MEMBERS

No members shall be permitted to address the Association unless they shall first have given their name and address, which shall be distinctly announced from the chair If desirable, the member may be required to go forward and speak from the platform

Failure to do special committee work shall cause the offender to forfeit a continuance of the same ap-

pointment, or a place upon any other, unless satisfactory excuse is offered

It is expected that every member will, in every available way, promote the interests of the medical profession as represented in the Association, and will conform to all its regulations in spirit and letter until they may be altered by the action of the body which formulated them.

CONDITIONS EXCLUDING FROM MEMBERSHIP

All societies that reject the Code of Ethics of the AMERICAN MEDICAL ASSOCIATION, or intentionally violate or disregard any article of the same, are thereby of their own choice debarred from membership

THE PREVIOUS QUESTION

When the previous question is demanded, it shall take at least twenty members to second it When the main question is put under force of the previous question and negatived, the question shall remain under consideration, the same as if the previous question had not been enforced

NEW BUSINESS

No new business, or resolutions by members, shall be introduced at the general session of the Association, except on the first and fourth days of the meetings

ELIGIBILITY TO OFFICE

In the election of officers and the appointing of committees by the Association and its President, *they shall be confined* to members present at the meeting, except in the Committee of Arrangements

MEDICAL AND SURGICAL EXHIBIT

There shall be no medical and surgical exhibit, under the authority or recognition of the AMERICAN MEDICAL ASSOCIATION, other than that made before the several Sections under the supervision of the Business Committee All that is new and of value to the scientific or practical physician can thus find an appreciative audience Experience has shown that all other exhibits detract from the work in Sections, and so lessen the attractiveness of the annual meetings to those whose presence is desirable

Signed H D HOLTON, *Chairman*
LEARTUS CONNOR
DANIEL E NELSON
BENJAMIN LEE

AMENDMENTS PROPOSED BY A MAJORITY OF THE COMMITTEE ON REVISION TO THE REPORT AS MADE BY THEM LAST YEAR AT MILWAUKEE

Amendment to be inserted between lines 28 and 29[1]

ANY Commissioned Officer of the Medical Staffs of the Army, Navy and Marine-Hospital Service may become a member of the ASSOCIATION by presenting to the Committee of Arrangements at any annual meeting his commission in that branch of service of which he is a member or a certificate that he holds such commission from the Surgeon-General, or officer authorized to act for him, and a receipt from the Treasurer of this ASSOCIATION showing that he has paid the annual dues

Amendment to be inserted in line 31 after the words "their society"[1]

Or if a member of the Public Service from the Surgeon-General or Officer authorized to act for him of the corps to which he belongs

Amendment to be inserted in line 134 after the word Committee[1]

With one person appointed by each of the State Medical Societies, and from each branch of the aforesaid Public Service

EXPLANATORY NOTE—It will facilitate understanding the proposed Constitution and By-Laws if the following considerations are kept in mind

1 The key-note to all the changes suggested is "the advancement of scientific medicine as represented in the Sections" The Sections include all the ASSOCIATION Hence, the elevation of the Sections to a more active participation in the conduct of affairs simply locates responsibility differently and, it is believed, more satisfactorily It will be noted that the Sections are given no power to act independently of the ASSOCIATION No act or recommendation of their representatives becomes binding upon the ASSOCIATION until the general body has so voted The Business Committee from the Sections simply thinks over the problems committed to it, and advises the ASSOCIATION in accordance therewith It is believed that this Business Committee is so constituted as to fairly represent the entire ASSOCIATION and the interests of the Sections The only additional duty imposed upon this Committee beyond that it already possesses is the nominating of the officers of the ASSOCIATION and recommending the place of meeting The officers and the place of meeting so obviously affect the prosperity of the Sections that it seems wise for them to make recommendations It is believed that the fact that all questions will hereafter be fully studied by representative committees of such character as to command confidence, will attract to the ASSOCIATION thousands who have hitherto stood aloof, will promote the feeling of fair play between individuals, and give assurance to all that hereafter no ill considered action will be taken by this great body

2 Radical changes are made in the conditions of membership It will be seen that but one kind of members is provided for To discriminate between the worthy and unworthy has been referred to the several State societies If these societies or the proper officer of one of the specified Medical Corps indorse an individual as worthy in their several States or respective Medical Corps, then the AMERICAN MEDICAL ASSOCIATION accepts them without question, and enrolls them among its members on their payment of the annual dues This membership can be retained indefinitely by the annual presenting of a certificate of good standing in the State society of which the individual is a member, and paying the annual dues Thus it is possible for every member of the profession in the North American continent to become and remain an active member of the ASSOCIATION No person can become a member of the ASSOCIATION who does not become a member of a State society or Medical Corps and retain his active membership therein It will be noted that the term, "State society," is made to include the Territories and the District of Columbia It also includes Mexico and Canada upon the same conditions as the States Distinguished gentlemen from other countries are cared for as guests either of a Section or the general ASSOCIATION

3 The general meetings of the ASSOCIATION are reduced to the shortest space possible consistent with the doing of the necessary routine work On the other hand, the Section meetings are lengthened to the greatest possible extent The reputation of the ASSOCIATION, its power to advance the bounds of medicine, its attractiveness to the tens of thousands of doctors, must lie in the Section activities Only here can be obtained adequate compensation for absence from active practice, with its necessary financial losses, for long and tiresome journeys, and for expenditure of a considerable sum from the scanty surplus of the average doctor's income

Meanwhile, it is believed that the new features provide for the more satisfactory transaction of all business that may come before the ASSOCIATION By adopting the document as presented, the ASSOCIATION will have provided for the study of every question by experts previous to its consideration by the ASSOCIATION It thus will be able to act with more tact and wisdom

It is believed that the adoption of the proposed organic laws will promote the best interests of the ASSOCIATION, of its Sections, of scientific medicine, of the several State societies, and of every intelligent practitioner of medicine, and hasten the organic unity of the profession of the entire North American continent As such, it is commended to the consideration of the ASSOCIATION

[1] The numbering of lines is necessarily omitted in the JOURNAL, they will be printed in the official document to be used at the meeting

CODE OF MEDICAL ETHICS AND ETIQUETTE OF THE AMERICAN MEDICAL ASSOCIATION

Report of Majority of Committee

PROEM

A code may be either penal or ideal A penal code is an authoritative compilation of laws and is enforced by the infliction of penalties Such are the civil and criminal codes of national, state and municipal governments

An ideal code is the crystallization of the best thought and sentiment of any considerable body of men who have for long periods been associated with a common purpose, with reference to the regulation of their conduct in their relations to one another and to society in general

Such a code forms an ideal standard, to the requirements of which each individual should strive to attain—a lamp to the feet of the young and inexperienced—a mirror into which the more mature, glancing, may be able to judge whether or not they are swerving from the paths of rectitude and honor

Ethics is that science which treats of human actions and mental affections considered as virtuous or vicious, right or wrong A code of ethics therefore takes cognizance of, and formulates rules of action of the most exalted character, founded on eternal principles of justice, as applicable to the special conditions of the class for which and the time at which it is formed Hence it follows that, from time to time, certain of its non-essential details may be modified without in any way impairing the solidity of its fundamental teaching Obviously the code adopted by a learned profession must be ideal rather than penal as it would be beneath the dignity of its members to bind themselves by penal restrictions On the other hand, those who become obnoxious to the punishment of the penal code of any existing government are *ipso facto*, unworthy of association with the members of such a profession Medical Ethics, as a science, is well worthy the study of all physicians, and should be included in the curriculum of every medical college The code which springs from its teachings is based upon the actual experience of the noblest members of the profession, from the earliest times down to the present, and contains the essentials for the successful and honored conduct of a medical career

Etiquette consists in the observance of a certain form of ceremonial between two or more persons in the conduct of affairs of frequent occurrence Unlike ethics it involves no distinct question of morals, but, as by due conformity to its requirements the prosecution of affairs is facilitated, friction diminished, misunderstandings obviated and intercourse rendered more agreeable, it can not be neglected by physicians any more than by other classes of society The peculiarly delicate and personal character of the relations of physicians to their patients naturally involves conditions which call for especial provision in this respect

PART I—MEDICAL ETHICS

CHAPTER I.

OF THE OBLIGATIONS RESTING UPON PHYSICIANS

ARTICLE I—*Of the Education of Physicians*

Of the momentous nature of the responsibilities devolving upon physicians there can be no question The issues of life and death hang upon the proper performance of their duties These responsibilities are only the graver and more enduring because there is no tribunal other than their own consciences to adjudge penalties for ignorance or neglect On this ark none should venture to lay presumptuous hands Manifestly the first duty of those who assume such responsibilities is to prepare themselves by a long laborious and faithful course of study for the practice of this difficult and recondite art

This course of study should be

1 Preliminary—This should include the ordinary branches of a liberal education, such as are taught in collegiate institutions which confer degrees in the arts, so-called, among which may be named languages, mathematics, literature, history, philosophy and logic Not until the memory has been thus stored with essential preparatory knowledge and the mental faculties have been trained to processes of correct reasoning, will the individual be in a position to comprehend the more abstruse science of medicine in all its branches, and to assimilate and utilize the immense amount of facts thrust upon the mind in the crowded curriculum of a medical school Not the least among the advantages of such an education in the humanities in preparation for purely technical study, is the ennobling and refining effect of intercourse with the cultured and learned, on the character and manners, by virtue of which that courtesy, propriety and dignity of demeanor, which are essential to the character of the true physician, as depicted in every code that has ever been written, become a second nature, requiring no enforcement by rule

2 Technical—This should embrace such earnest and prolonged study of medicine in all its departments as will render the student reasonably familiar, not only theoretically but practically, with the universally recognized fundamental branches of the science and art

Equipped with this degree of mental furnishment and technical skill, and with nothing short of this, is the physician ready to enter, with a clear conscience and a proper self confidence, upon the discharge of the responsible duties of a practitioner of medicine

ARTICLE II—*Of the Duties of Physicians to Their Patients*

SECTION 1—Being thus possessed of the requisite knowledge and skill for the treatment of disease, and also of the sanction of government for their employment, physicians should consider these acquisitions as sacred talents committed to their trust, and should use them diligently, honestly and solely for the benefit of their patients It should be manifest to all that they do not suffer their own ease, comfort, pleasure, profit, advancement or dignity even, to interfere with the discharge of this primal fundamental duty

SEC 2—The authority of the physician in the sick room is absolute and autocratic Like all powers its possession carries with it the obligation not to abuse it, but rather to exercise it as gently and unobtrusively as is consistent with the good of the patient

SEC 3—The familiar and confidential intercourse to which physicians are admitted in their professional visits, should be used with discretion and with the most scrupulous regard to fidelity and honor The obligation of secrecy extends beyond the period of professional services, none of the privacies of personal and domestic life, no infirmity of disposition or flaw of character observed during the professional attendance should ever be divulged by the physician except when he is imperatively required to do so The force and necessity of this obligation are indeed so great, that professional men have, under certain circumstances been protected in their observance of secrecy by courts of justice Physicians should discourage as much as possible, however, the needless disclosure of family concerns, the knowledge of which is not essential to successful treatment

SEC 4—Physicians should not be forward to make gloomy prognostications, because they savor of empiricism, by magnifying the importance of their services in the treatment or cure of the disease But they should not fail on proper occasions, to give to the friends of the patient timely notice of danger when it really occurs, and even to the patient himself if absolutely necessary This office, however, is so peculiarly alarming when executed by them, that it ought to be declined whenever it can be assigned to any other person of sufficient judgment and delicacy

SEC 5—Physicians ought not to abandon a patient because the case is deemed incurable, for their attendance may continue to be highly useful to the patient, and comforting to the relatives, even in the last period of a fatal malady, by alleviating pain and distress, and by soothing mental anguish

ARTICLE III—*Circumstances under which Physicians may properly decline to render Their Services*

SECTION 1—While the duties of physicians to their patients are thus imperative, there are on the other hand, reciprocal obligations of patients to their physicians of so obvious a character, that their studied neglect will justify the latter in declining to continue attendance on a family or a case

SEC 3—Such are The habitual refusal or neglect, on the part of those who can not plead poverty as an excuse, to remunerate a physician for services rendered, the refusal or studied neglect on the part of a patient or the family of a patient, to carry out the instructions which the attendant deems essential, the surreptitious use by the patient of remedies not prescribed by, or disapproved of, by the attendant, and the surreptitious introduction of another physician, either as the family adviser, or during the progress of a case

CHAPTER II

OF THE RELATION OF PHYSICIANS TO THE PROFESSION AND TO THEIR COLLEAGUES

ARTICLE I.—*Duties for the Support of Professional Character*

SECTION 1.—The possession of the privileges and immunities appertaining to membership in the medical profession imposes the obligation to maintain its dignity and honor, to exalt its standing and to extend the bounds of its usefulness. It is incumbent, therefore, upon its members to make themselves familiar with this and similar treatises in which are epitomized the views of the best and noblest of its votaries in all the ages, and to shape their conduct in accordance with the settled principles therein laid down. It must be constantly borne in mind, however, that the profession exists not for the maintenance of its own dignity and honor, but for the benefit of humanity. Its true dignity will therefore be best promoted by an unsullied life and by the strict observance of the requirements of the opening articles of this Code, namely, the acquirement of such an education as shall make its members at least the peers of those of the other learned professions, and single-hearted devotion to the welfare of those who seek their services. Frequent and fulsome allusions to this subject, however, as well as claims of unusual self-sacrifice and beneficence on the part of the profession, especially in print, are in bad taste, and only subject those who make them to the ridicule of thoughtful men.

SEC. 2.—It is derogatory to the dignity of the profession to resort to public advertisements, or private cards or handbills inviting the attention of individuals affected with particular diseases—publicly offering advice and medicine to the poor gratis, or promising cures, or to publish cases and operations in daily prints, or suffer such publications to be made, to invite laymen to be present at operations, to boast of cures and remedies, to adduce certificates of skill and success, or to perform any other similar acts. These are the ordinary practices of empirics, and are highly reprehensible in physicians. It shall not be considered as a violation of the spirit of this section, however, for physicians engaged in the work of medical education, either singly or associated in colleges, or for physicians practicing in hospitals, whether private or public, general or special, to announce the fact or allow it to be announced to the profession in the advertising pages of strictly medical journals, or for physicians devoting special attention to one of the recognized special departments of medical practice to note the fact on their signs or private cards.

SEC. 3.—Equally derogatory to professional character is it for physicians to hold patents for secret nostrums. For, if such nostrums be of real efficacy, any concealment regarding them is inconsistent with beneficence and professional liberality, and if mystery alone give them value and importance, such craft implies either disgraceful ignorance or fraudulent avarice. It is also reprehensible for physicians to give certificates attesting the efficacy of secret remedies.

ARTICLE II.—*Of Consultations*

SECTION 1.—Consultations should be promoted in difficult or protracted cases as they give rise to confidence, energy and more enlarged views in practice. A request for a consultation by patients or their friends should not be considered as implying distrust of or dissatisfaction with the attendant. Nor should it be assumed that the consultant is called in because he is the superior in knowledge or skill of the attendant, or that it is his function to pass judgment on the treatment which has been pursued. The true ground is simply the benefit which may accrue to the patient by bringing the judgment of two or more minds to bear upon the case.

SEC. 2.—A consultation being requested either by the physician or by the family or patient, it is the right of the former to select the consultant. It is equally the right of the physician thus called upon to decline the consultation, unless in exceptional emergencies where life is immediately at stake. A thorough education, preliminary, scientific and technical, furnishes the only presumptive evidence of professional abilities and acquirements, and ought to be the only acknowledged right of an individual to the exercise and honors of his profession. Nevertheless, as in consultations, the good of the patient is the sole object in view, and as this is often dependent on personal confidence, no intelligent practitioner, who has a license to practice from some medical board of known and acknowledged legal authority, and who is in good moral and professional standing in the place in which he resides, should be refused consultation, when it is requested by the patient.

SEC. 3.—Consultants should observe the most scrupulous regard for the character and standing of practitioners in attendance, carefully avoiding any insinuation which could impair the confidence reposed in them or injure their reputation.

CHAPTER III

OF SPECIAL DEPARTMENTS IN MEDICAL PRACTICE

ARTICLE I.—*Of the Necessity for Specialties*

SECTION 1.—The advantages which have accrued to the science and, in a still more marked degree, to the art of medicine, and hence to humanity, from the division of its practice into a number of departments can not be gainsaid. Differentiation in study and labor of whatever kind is the test of civilization. The field of medical knowledge is now so vast that no one mind can compass it in all its details. Nor can any one hand obtain the dexterity essential for the successful performance of all the delicate and daring operations of modern surgery.

ARTICLE II.—*Of the Education of Specialists*

SECTION 1.—Specialists should not be something less than general practitioners, but general practitioners and something more. Without omitting one jot or one tittle either of the preliminary or of the technical education insisted upon as essential for the physician, they should superadd to this a period of general practice, and then, upon this broad foundation of theoretical and practical knowledge, should build the superstructure of the special art for which they feel themselves best qualified by natural ability.

ARTICLE III.—*Of Specialists as Consultants*

SECTION 1.—As a consultation is the conjoint investigation of a case by several practitioners with a view to its conjoint treatment, the responsibility being equally divided between them—they equally sharing the credit of success as well as the blame of failure—the mere introduction of a patient to a specialist by the attendant, with the communication of such facts in regard to the personal or family history as may assist in deciding whether it is for the best interests of the patient that the specialist shall assume entire control and management of the case, does not, in any true sense, constitute a consultation, and should not therefore be subject to the same limitations.

SEC. 2.—It is the obvious duty of general practitioners, when cases come under their care for the successful management of which they have not had the requisite training, or do not possess the necessary facilities and appliances, to recommend and introduce such cases to a competent and reputable specialist, and thus prevent them from drifting into the hands of charlatans.

CHAPTER IV

OF THE COMPENSATION OF PHYSICIANS

ARTICLE I.—*Of Fees*

SECTION 1.—Under existing conditions, physicians are dependent for their livelihood on fees received from their patients. The attempt to gloss over this fact under the pleasing fiction of the voluntary *honorarium* savors rather of charlatanry than of professional dignity. In justice to themselves and their fellow practitioners, therefore, physicians should present their claims for remuneration at stated and frequent intervals, and, if payment is refused or unreasonably delayed, should not hesitate to take legal measures to compel the same.

SEC. 2.—A fee-bill may properly be adopted by the physician of any circumscribed locality as a general guide in regard to the standard of charges, but should be considered simply as establishing a *minimum* rate for patients in good circumstances.

ARTICLE II.—*Of the Business Relations of Physicians*

SECTION 1.—It should never be forgotten, however, that the relation of practitioners of medicine to their patients is not that of tradesmen to their customers. Such competition as is considered honorable in business can not exist between physicians without diminishing their usefulness and lowering the standard of the profession. Equally unprofessional is a resort to the devices of the trades union and the boycott.

The attempt to obtain the practice of others by underbidding is extremely disreputable. It especially behooves

physicians of large means to be on their guard against the temptation from personal motives, to remit or diminish fees in the case of prosperous patients as great hardship may thus be worked to their less fortunate brethren Physicians should exercise care in entering into contracts with corporations companies or societies, that the compensation agreed upon is such as to elevate rather than depress the local standard of remuneration for similar medical services

Sec 2—As in consultations the conditions are such as involve unusual responsibilities, at least a double fee should be charged by both attendant and consultant

Sec 3—Poverty and professional brotherhood should always be recognized as presenting valid claims for gratuitous services, but neither institutions endowed by the public or by individuals societies for mutual benefit, for the insurance of lives or for analogous purposes, nor any profession or occupation can be admitted to possess such privileges Nor can it be justly expected of physicians to furnish certificates of disability to serve on juries, or perform military duty, or to testify to the state of health of persons wishing to insure their lives, to obtain pensions, or the like, without a pecuniary acknowledgment

ARTICLE III—*Of Fees in Vicarious and Casual Attendance*

SECTION 1—In the event of the enforced absence or disability of physicians for brief periods, their colleagues should cheerfully and gratuitously attend to their practice and, on their return should furnish a statement of services rendered in order that they may collect the fees therefor A physician, however, contemplating a protracted absence can not reasonably expect the extension of such a courtesy

Sec 2—In obstetrical and important surgical cases, which give rise to unusual fatigue, anxiety and responsibility, it is just that the fee should be awarded to the physician who actually renders the service If, in a case of confinement, the physician who has been engaged arrives after the birth of the child under the management of a casual attendant, but before the delivery of the placenta, the fee should be equally shared by the two physicians

CHAPTER V

OF THE DUTY OF PHYSICIANS TO THE STATE

ARTICLE I—*Of General Duties*

SECTION 1—As good citizens it is the duty of physicians to be ever vigilant for the welfare of the community, and to bear their part in sustaining its institutions and burdens, they should also be ever ready to give counsel to the public in relation to matters especially pertaining to the profession as on subjects of medical police, public hygiene and legal medicine

Sec 2—It is their province to enlighten the public in regard to quarantine regulations, the location, arrangement and dietaries of hospitals, asylums, schools prisons and similar institutions, the protection of water supplies, the medical police of towns, sewerage and drainage, and the prevention of epidemic and contagious diseases When pestilence prevails, it is their duty to face the danger, and to continue their labors for the alleviation of suffering and saving of life, even at the jeopardy of their own lives

ARTICLE II—*Of Special Duties of Physicians as Experts*

SECTION 1.—Medical men should also be always ready, when called on by the legally constituted authorities, to enlighten coroner's inquests and courts of justice on subjects strictly medical, such as are embraced in the science of medical jurisprudence But in these cases, and especially where they are required to make a postmortem, it is just, in consequence of the time, labor and skill required, and the responsibility and risk which they incur, that the public should award them adequate compensation

Sec 2—Physicians have a right to expect pecuniary acknowledgment from the State for the time and labor which they expend in making out returns for sanitary and statistical purposes, but they should not consider the neglect of the State to recognize the justice of this claim a ground for refusing to make this important contribution to the public weal

PART II—MEDICAL ETIQUETTE

CHAPTER I

OF COURTESY BETWEEN PHYSICIANS

ARTICLE I—*Of the Nature of Etiquette*

SECTION 1—The etiquette which should prevail between physicians in their professional intercourse and contact is founded upon the dictates of common sense and the requirements of common courtesy

Its strict observance will not fail to command the respect and goodwill of other members of the profession, and to promote that sense of mutual confidence and brotherhood which is so eminently desirable

ARTICLE II—*Of Professional Services of Physicians to Each Other*

SECTION 1—Practitioners of medicine are entitled to the gratuitous services of any one or more of the faculty residing near them whose assistance may be desired

Physicians when ill are usually incompetent judges of their own cases, and the natural anxiety and solicitude which they experience at the sickness of those who are peculiarly dear to them tend to obscure their judgment, and to produce timidity and irresolution in practice Under such circumstances, medical men are especially dependent upon each other, and kind offices and professional aid should always be cheerfully afforded whether to themselves or to those members of their families who are immediately dependent upon them for support

Sec 2—In many instances, however, a substantial recognition of such services may be both offered and accepted without violation of professional courtesy on either side

Sec 3—Physicians should select some one member of the faculty as their family attendant, to whom the same loyalty, confidence and respect should be accorded as they expect from their own patients

ARTICLE III—*The Etiquette of Consultations*

SECTION 1—A consultation having been decided on, the attendant or a member of the patient's family should convey to the physician selected the request for the meeting, leaving the determination of the hour to the consultant

Sec 2—The attendant should endeavor to reach the house in advance of the consultant in order to prepare the mind of the patient for the ordeal, as well as to receive the consultant and briefly to communicate such salient facts as may save the time of both in the sick room

Sec 3—The attendant should precede the consultant in entering the patient s room and should briefly examine the case in order to restore confidence to the patient so that questions may be the more intelligently answered as well as to inform himself of the progress of the case since his last visit The consultant should then be requested to make a full and satisfactory examination of the case, the attendant calling attention to any noteworthy or perplexing features which may have escaped the notice of the consultant On the conclusion of the examination, they should retire to a private place for deliberation, the attendant being the last to leave the room

Sec 4—The opinion of the attendant should be delivered first When there are several consultants they should deliver their opinions in the order in which they have been called No decision, however, should restrain the attending physician from making such variations in the mode of treatment as any subsequent unexpected change in the character of the case may demand Such variation and the reason for it should be carefully detailed at the next meeting in consultation The same privilege and obligation belong also to the consultant if sent for in an emergency, when the regular attendant can not be obtained

Sec 5—The attendant should communicate the directions agreed upon to the patient or his friends Any opinions which it may be thought proper to express to the family may be communicated by the consultant But no statement or discussion should take place before the patient or his friends, except in the presence of all the faculty attending, and by their common consent, and no opinions or prognostication, should be delivered which are not the result of previous deliberation and concurrence

Sec 6—In case of the unavoidable delay of one of the parties to a consultation, custom does not require the physician present to wait more than fifteen minutes after the time fixed At the expiration of that period it will be the duty of the attendant if present, to see the patient and prescribe, but under similar circumstances the consultant should retire, unless informed that the condition of the patient is so alarming as to require instant attention, or in case the consultant is at a considerable distance from home when the patient may be seen, and the immediate emergency met, or such examination made as may be deemed requisite Information of such action, with a statement of conditions found and opinions arrived at, should be left for the attendant in writing and under seal Otherwise, the consultant should await another appointment

ARTICLE IV.—*The Etiquette of Occasional and Accidental Attendance*

SECTION 1.—The same scrupulous regard for the reputation and feelings of their brethren which is binding in consultations should regulate the conduct of practitioners, when in a sudden emergency or for any reason, professional or otherwise, they are brought into confidential relations with the patients of other physicians

SEC. 2.—A physician should not take charge of or prescribe for a patient who has recently been under the care of another member of the faculty in the same illness, except in the case of sudden emergency, or when the latter has relinquished the case, or has been formally dismissed and properly compensated

SEC. 3.—A physician called to an urgent case, because the family attendant is not at hand, should resign the care of the patient immediately on the arrival of the latter

SEC. 4.—A physician called to the patient of another practitioner in consequence of the sickness or absence of the latter, should on the return or recovery of the regular attendant and with the consent of the patient, surrender the case

SEC. 5.—When, in the case of sudden illness, or of recent accident, several physicians are simultaneously summoned, the patient or family should indicate which one they prefer. Otherwise, courtesy should assign the patient to the first who arrives, who should select from those present such additional assistance as may be needed. In all such instances, however, the practitioner who assumes the management should insist that the family physician be called, and, unless further attendance be requested should, with the others present, resign the case on the arrival of the latter.

SEC. 6.—A physician called to a case of sudden or accidental death not occurring in his own practice, should direct that the usual attendant be at once informed thereof, in order that the latter may arrange for an autopsy, if advisable, and perform any other professional services required in such circumstances.

CHAPTER II

OF DIFFERENCES BETWEEN PHYSICIANS

ARTICLE 1.—*Of Avoidance of Misunderstandings*

SECTION 1.—A physician should always be slow to suspect a colleague of intentional slight, injury or wrongdoing, inasmuch as a full knowledge of the facts and circumstances may satisfactorily explain conduct which at first seems offensive or selfish.

ARTICLE II.—*Of Arbitration*

SECTION 1.—Should diversity of opinion or opposition of interest, however, unfortunately lead to disagreement and estrangement between individual members of the profession, the case should not be left to create or to foster prolonged animosity but should be referred at once, privately, to the arbitration of a suitable number of physicians or a court-medical, whose decision should be final.

SECTION 2.—As, in consequence of the intimate and confidential character of the relation of physicians to their patients there exist numerous points in medical etiquette through which the feelings of medical men may be wounded in their intercourse with each other, which can not be understood or appreciated by general society, neither the subject matter of such differences nor the decision of the arbitrators should be made public.

ARTICLE III.—*Of Seniority*

SECTION 1.—Seniority among the practitioners of any city, town or district is determined not by age, but by the period of public and acknowledged residence as a practicing physician in the same.

SEC. 2.—At informal meetings and on public occasions, courtesy accords the position of prominence to the senior.

SEC. 3.—Physicians newly establishing themselves in practice in any place should, as soon as practicable, call upon the resident physicians, or otherwise notify them of their arrival, and of their desire to cultivate fraternal relations with them.

HENRY D. HOLTON, Chairman
LEARTUS CONNOR,
DANIEL T. NELSON,
BENJAMIN LEE

Blank Applications for membership in the ASSOCIATION, at the JOURNAL office.

SOCIETY PROCEEDINGS

American Electro-Therapeutic Association

The Third Annual Meeting Held in Chicago, Sept. 12, 13 and 14, 1893

AUGUSTIN H. GOELET, M.D., President

(*Continued from page 468*)

AFTERNOON SESSION—THIRD DAY—SEPTEMBER 14.

The meeting was called to order at 2.30 P.M.

CHAS. G. CANNADAY, M.D., of Roanoke, Va., Member of AMERICAN MEDICAL ASSOCIATION, American Electro-Therapeutic Association, British Gynecological Association, London, Pan American Medical Congress, etc., read a paper on

THE TREATMENT OF SUBINVOLUTION BY ELECTRICITY.

Sir James Simpson's "Subinvolution", Scanzon's "Chronic Parenchymatous Metritis," Klobs' "Habitual Hyperemia, with Profuse Proliferation of Connective Tissue," Edis' "Metritis," Hodges' "Irritable Uterus," Lisfrancs' "Engorgement," Kiwisch's "Infarctus," and Noeggerath's "Diffuse Interstitial Metritis," or any other name that may describe the enlarged and engorged condition of the uterus only recalls to the practitioner, up to a few years since, the stubborn and unyielding condition he has to treat. To Sir James Simpson we are more indebted than to any other for accurately defining and calling attention to its frequency and treatment. One of the first to describe its macroscopic and microscopic appearance was Snow Beck, in 1851.

Its etiology is interesting in the extreme. Everything that could have been credited with producing a pathologic condition of the pelvic organs has been claimed as an exciting cause, but it seems that a large number of those cases coming under observation have followed abortions, lacerations, twin-pregnancies, and similarly enlarged pregnant uteri (viz. large children, hydramnios, etc.), and in those delicately constituted as to uterine development. This will cover a wide field, and to this might be added another very frequent cause, viz. The practice of using ergot at some time during labor, which stimulates the contraction of the unstriped muscular fiber, producing a quasi-tetanoid spasm of the uterus, which subsequently fails to contract sufficiently to induce involution. As to histology. The bulk of the investigators concede that the uterus consists of unstriped muscular fibers in the highest state of development, varying in length from one one-hundred-and-tenth to one-fortieth of an inch, as it is found in the unimpregnated or gravid state, also yellow elastic, fibrillar and homogeneous connective tissue, round, spindle-shaped, and irregular cells (Thomas' elementary fusiform fiber cells) serous membrane, mucous membrane, nerves, blood vessels and lymphatics.

During gestation, the muscle cells enlarge to ten times their size in the unimpregnated uterus. All the remaining anatomic structures of the uterus during gestation are enlarged. After parturition, the uterus should rapidly decrease, until in four to six weeks it has attained its normal size. This change is the result of the fatty degeneration of the muscular fiber, with the subsequent absorption of this fatty material, and its removal from the uterus. This is brought about by the impaired nutrition, the result of the chronic contraction of the unstriped muscular fiber, which contraction should be immediate and permanent after delivery, otherwise, the nutrition of the cells is not impaired, foundation for excessive amount of connective tissue is laid and normal involution can not obtain. As all writers recently have occasion to regret, our pathology is very scanty on a disease which has had a recognized position in gynecology for the last forty-five years. It is evident to all observers that there is an excessive amount of tissue present and that there is also quite a defective condition of both the vascular and lymphatic systems. No clear and concise limits can be definitely fixed between the pathology of some forms of chronic metritis and subinvolution.

Mary Putnam Jacobi, who, under a very careful study of the subject, found the muscular fibers enlarged, with nuclei disappearing, and smaller fibers with indistinct central nuclei, others still smaller in which the nuclei were distinct, while in another variety no nuclei were discovered, but granular and oil globules were found and that the wasting of the cell began in the protoplasm and ended in the nucleus. She found among these fibers nucleated connective tissue cells and amorphous tissue. The blood vessels and lymphatics were very much enlarged and intimately connected

with the muscular tissue, which she considers a strong diagnostic point from chronic metritis, as herself and De Sinety have shown, in the latter, a peri-vascular condition is present Its diagnosis is generally easy, when we remember that an abortion or pregnancy must be present as a starting point Hansen finds that involution extends over a period of twelve weeks, but that in two thirds of the cases the uterus has returned to normal in from six to ten weeks Weakness of the back, excessive *lochial* discharge, or the appearance of menorrhagia may be the most important symptoms found during the puerperium Evidently, in the first stage, we have hyperemia and congestion A large *flabby uterus, with thickness* of walls increased, and the sound reveals an enlarged uterine cavity, the mucous membrane bleeds freely Whether this be chronic metritis or subinvolution uteri, following abortion or confinement, matters little in the treatment

As to treatment That, other than electricity, will only lightly be touched upon As prophylactic clearing well the uterus of clots, the use of weak antiseptic vaginal injections refraining from use of ergot, or any of its kindred drugs at any time in labor, or, if used during labor, to be continued *for several days after* labor at suitable times to induce and maintain contraction of unstriped muscular fiber, and to induce physiologic malnutrition, so necessary for the fatty degenerative process common in normal involution Tonics, baths and drugs, hastening absorption with nutritious diet will accomplish much in building up the system Vaginal injections of hot water *110 or 115 degrees*, using three or four gallons once daily, with pledgets of cotton every third night, inserted up the vagina saturated with anhydrous glycerin and boro-glycerid with the application of iodized phenol on a cotton wrapped probe or better still, by a few drops injected into the cavity of the uterus with an intra-uterine syringe, provided the os is patulous, will all hasten the cure If the os is very much congested, a Buttles scarificator plunged into the cervix and the congestion relieved in this way will do much good toward aiding a cure But the greatest amount of good can be accomplished in the least time by the proper application of electricity The detection of subinvolution is generally not accomplished as early as the tenth day, from the fact that *any symptom* referable to this is not generally attributed to this cause, but if it is detected at so early a stage, that is, at ten days and the intra-uterine dimensions is found to be ten centimeters, and much tenderness does not exist, we should use the medium Engleman coil, having a length of 200 meters and a diameter of *seven-tenth* millimeters, with the bipolar vaginal electrode, after the manner suggested by Apostoli, using as powerful current as the patient is able to stand to accomplish the object This to be continued for five minutes, then to be discontinued for ten minutes, with the electrode in same position, when the current should be re applied for a period corresponding for same time, when the electrode should be removed If a more powerful effect is desired, the intra uterine bipolar method should be tried, having the proximal pole of the intra uterine electrode stop at the os and the distal as far toward the fundus as it will reach, pressing it alternately to posterior, anterior and lateral portions of uterus This to be used with Engleman's coarse coil having a diameter of one and four-tenths millimeters and a length of sixty-six meters with a strong current But in failing to effect involution in this manner, as will often be the case, owing to such a sensitive condition of parts, or to the infiltration of tissue being so abundant and so organized as to preclude any certain results from the treatment we must adopt another The writer is mainly influenced by Hansen's observations as to diagnosis of subinvolution and if he finds at the second week a uterus varying from eight to thirteen centimeters at third week from seven and five tenths to ten and five-tenths, and at the *fourth* week from seven to nine centimeters and fifth week from six to nine centimeters, *it* is concluded he has subinvolution to deal with, and, provided symptoms are present as above described the case is treated on a different plan, by aiming, first to reduce the engorged and congested condition, secondly, to absorb hyperplastic elements and thirdly to restore tone to muscular and vascular structures This consists of first positive galvanic intra uterine application of at least thirty milliampères from eight to ten minutes, and if much tenderness exists and pain is induced, to be followed by the vaginal bipolar application of the faradic current from a coil having a diameter of .225 millimeters, and having a length of 600 meters, after the method as described by Engleman By this means the uterus is relieved of engorgement the unstriped muscular tissue composing the uterine walls are strengthened, and the walls of the blood vessels are restored to their normal contractile powers The capillaries are relieved of their hyperemic condition and the process of involution is in every way aided Bipolar intra-uterine faradization must be carried out to be effective in this instance by the bipolar intra uterine sound

If the subinvolution has passed the stage of active congestion we may hasten involution by using the negative pole of the galvanic current—intra uterine—especially if the uterus presents a hardened condition In several instances in which ergot was freely used during labor, there has been used the daily application of the faradic current to uterus for seven or eight days, as used by Trippier and Apostoli of Paris and in each instance with the happiest results, and I am of the opinion that this should be used in all cases where ergot has been freely used during labor, strict antisepsis being carried out in each instance

By this method described, I am satisfied that subinvolution uteri can be cured in one-half of the time consumed by any other means than electrical

DISCUSSION

Dr Dickson said he had had good results from the faradic current in the treatment of subinvolution

Dr Hayes felt that galvanism did more towards starting up a new retrograde metamorphosis than the faradic current although both are beneficial But in subinvolution, there is an arrest of that physiologic change by which the organ is reduced from a weight of about three pounds at the time of confinement to a weight of about three ounces, as it is in the unimpregnated condition In his estimation, no agent is superior to electricity in starting anew this process, and clinical experience shows that this has accomplished more than curetting or the surgeon's knife He would employ the positive pole because there is frequently an increased menstrual flow, and there is also a flabbiness and a condition of undue moisture which seems to indicate this pole He rarely employed over forty or fifty milliampères, given from five to eight minutes at intervals of four or five days

Dr Sprague thought it made very little difference whether intra uterine galvanic treatment or bipolar faradization was employed, we can depend upon both to give relief His results had been more rapid when he had given sittings of fifteen minutes on alternate days

Dr Massey strongly commended the method He saw many acute cases of this kind in consultation, but very few in private practice unless they had lasted for many years At present he was disposed to return to the former belief that the relaxed uterus is the cause of very many of the reflex symptoms observed in women He uses the faradic current chiefly in cases which have existed not over six months If there be such a thing as a specific, it is electricity for subinvolution—the faradic current in recent cases, and the galvanic current for the more chronic ones Ergot frequently causes irritation and aggravates the condition Subinvolution, he thought, was almost always due to a microbic invasion of the uterus at the puerperal period If it be due to the gonorrheal germ the case will prove most obstinate, but other cases will be found quite amenable to this treatment

Dr A Lapthorn Smith added his testimony to the value of the continuous current in subinvolution He had not employed the interrupted current very much, although no doubt by the contraction of the muscular tissue which it produces, the uterus could be made to contract firmly upon the nutrient arteries, thus leading to fatty degeneration and absorption He agreed with the preceding speaker that subinvolution was very largely due to septic infection occurring at miscarriages or at full term We are especially apt to have this after abortions, because Nature is not prepared to carry out this retrograde process as she *is* at the completion of the normal period of gestation

He had had more experience with the treatment in alveolar hyperplasia viz Where the uterus is too deep, owing to a deposit of fibrous tissue between the layers of muscles In such cases, faradism is not effective, the continuous current is necessary It acts as calomel does when applied to the cornea i e, by exciting the activity of the absorbents No matter how performed he was certain the depth of the uterus could be reduced from day to day by negative galvanization

Dr Cannaday, in closing the discussion said that if the subinvolution had existed for a year or more the congestion will have *in* large measure subsided, and therefore greater benefit is likely to accrue from the use of negative galvani-

zation He wished to emphasize the fact that he thought ergot had much to do with the production of subinvolution, owing to the tetanoid condition it produces in the muscular fiber In recent cases, faradization is more active, but later on, it is of little avail except the current be from the fine coil

DR PIAM S HAYES of Chicago, then demonstrated by means of a eudiometer the amount of gas evolved from water during electrolysis This amount is somewhat in excess of that occurring in the uterus because a portion of the current is expended in decomposing the salts found in the tissues

This demonstration served as an introduction to Dr Hayes' description of

A NEW INTRA-UTERINE ELECTRODE

By PIAM S HAYES, M D, Professor of Electro-Therapeutics, Chicago Policlinic

I had employed the Apostoli method of the intra-uterine use of galvanic electricity for but a short time when my attention was called to the amount of gas liberated around the intra uterine electrode, and that the presence of the electrode in the cervical canal served as an obturator, preventing the escape of the gas which is formed

In one of my cases, that of a multipara, who, by repeated childbearing, had so large and patulous a cervical canal that the intra uterine electrode did not fully occlude it, I noticed the escape of gas by the side of the electrode in the form of a froth I also repeatedly noted the fact that the removal of the intra-uterine electrode was followed by the same froth, either with or without color, according as the introduction and removal of the electrode had been attended with sufficient traumatism to produce a slight hemorrhage or not Occasionally the escape of the gas was attended with a slight sound, such as would have attended the forcing of soap suds through a small orifice The escape of the gas with sufficient force to produce a noise suggested to me the probability of the presence of gas under pressure within the uterine cavity In order to demonstrate this, I have at times, after the employment of Apostoli's method, introduced the blades of a uterine dilator and opened them slightly and have seen as much as a drachm of bloody froth escape from the uterine cavity Experience soon demonstrated that when the gas was allowed to escape from the uterine cavity by means of the dilator or a uterine irrigator, the post-operative pain was decidedly lessened My experience in this regard, with report of case, was embodied in a paper which was read before the Tri-State Medical Society at their meeting at Chattanooga two years since

The method of providing a way for the gas to escape after electrolysis was an improvement on the method as described by Apostoli unless, perchance, it may be proven, that the post-operative pain is mainly due to uterine contractions excited by the gas which acts as a foreign body within the uterus and these contractions produce a decidedly therapeutic action on the uterine tumor That this claim has been made by any electro-therapist who has made use of this method is unknown to me, for I have failed to see any mention of it in the literature bearing on the subject Granted that the post-operative contraction is of therapeutic value, the query remains, Is the benefit derived from such contractions excited by the presence of gas of sufficient value to run the risk of forcing the contents of possibly diseased tubes or even uterine mucus into the abdominal cavity?

That the galvanic current causes gas to be liberated—hydrogen from the negative pole and oxygen and chlorin from the positive pole—when the fluids and tissues of the body are subjected to electrolysis, is an undisputed fact The amount of gas liberated from either pole by means of 100 milliampères of current passing for a definite period of time through water can readily be determined by means of a properly constructed eudiometer, which instrument becomes then a coulombmeter, 100 milliampères passing for five minutes through acidulated water will liberate 7 5 cubic centimeters of the mixed gases This is somewhat in excess of the amount that would be liberated in intra-uterine electrolysis, because here we have a portion of the electrolytic energy exerted in decomposing the salts and organic compounds found in the tissues Even if the gas liberated should be but one-half of the amount liberated in our eudiometer with acidulated water, it would still give us 1 25 cubic centimeters of oxygen in five minutes, which time is frequently consumed in intra-uterine electrolysis

The removal of gas after the electrolysis has been completed has been proven, by clinical experience, to be of value, but there remains the fact of a rapid evolution of gas within a muscular cavity that has three openings—the Fallopian tubes and the cervical canal, the last of which may be quite thoroughly occluded by the intra-uterine electrode, so the accident which we wish to avoid by the removal of the gas is quite likely to have occurred during electrolysis and before the method above described for the removal of the gas could have possibly been employed These considerations, in connection with the desire to produce an electrode that could readily be rendered aseptic, that would be comparatively easy of introduction, and that could be made to act within the uterine cavity and at the same time be without action on the cervical canal, caused me to formulate the following as the ideal of an intra uterine electrode

The active part of the electrode should be of platinum and flexible There should be a means of exit for the gas generated around the active part of the electrode and it should be so constructed as to sustain a boiling temperature, or be uninjured by being subjected to the action of an antiseptic solution Should the electrode become clogged with blood or mucus so as to prevent the exit of the gas, a means should be provided for clearing it while in situ while the current is passing, and should be so insulated that the cervical canal should not be subjected to the action of the current

The electrode I now present to you is the attempt at the embodiment of this ideal This electrode has now been in use for over a year and has proven to be of value in meeting the indications herein detailed It consists of a straight or slightly curved metal tube covered with hard rubber To the end of the tube is soldered a spiral of especially tempered platinum ribbon which terminates in a bulb of platinum The spirals of the platinum ribbon are separated so as to allow the entrance of liquids and gases into the interior of the spiral, which is continuous with the tube An oblong fenestra is made in the tube at the point that will be just external to the cervix, when the electrode is introduced The proximal extremity of the electrode is bent at an obtuse angle and is arranged for attachment to the battery An opening at the angle permits the introduction of a stylette, by means of which the tube can be cleared of accumulated mucus The stylette may also be used to maintain the form and give rigidity to the electrode during introduction The edges of the platinum spiral are made smooth and slightly rounded so as not to inflict injury on the soft parts The screw-like arrangement of the spiral aids materially in the introduction of the electrode, for as soon as the electrode is engaged in the cervical canal a rotation of the instrument causes it to advance The material of which the electrode is constructed allows of its being boiled, or being placed in alcohol, or some like aseptic solution

After using the electrode, I remove the mucus, blood, etc, which adheres to the spiral, by switching it rapidly through water and allowing the water from a faucet to run through the tube After this, the electrode is put into a test tube partly filled with water, with the platinum point down and the water brought to the boiling temperature and kept there for some minutes Then it is placed in another test tube containing alcohol and allowed to remain till needed To Mr Warner of the McIntosh Company, whose technical skill and perseverance has aided materially in the production of this electrode, much praise is due

I have entered thus fully into the details which prompted the construction of this electrode because it attempts to accomplish that which is entirely new, viz, the elimination of gas as it is generated by electrolysis into the uterine cavity In this particular, the electrode is a pioneer in a new field

The testimony of those who have used it, is that while it does not wholly prevent the post-operative pain in every case, it does so in a great degree in the majority of cases

Intra-uterine electrolysis is not without danger, even in the hands of the most conservative, and any instrument that will lessen the danger of setting up a peritonitis or of relighting the fires of an old one, should find a permanent place in our armamentarium

DISCUSSION

DR GEHRUNG said that when he began to use the Apostoli method at the time it was first promulgated, he made the same observation regarding the accumulation of gas within the uterus He employed puncture at that time, and found that the gases accumulated within the tumors, and formed the basis of future abscesses He had seen this also in the practice of others At that time he constructed a hollow electrode, which is illustrated in Dr Massey's book, and which consists of a trocar needle in a silver tube, open

at both extremities, and perforated with holes so that when the electrolysis has been applied through the trocar, the trocar may be removed, and the accumulated gas in the tumor allowed to escape through the cannula which is retained in position as long as deemed advisable It was found that fluids sometimes escaped for days after the operation, showing that the effect of the electrolysis lasts for some time after the application In one case, the cannula was left in for twenty one days The same method he used afterwards in the uterus in a similar way to that described in this paper

Dr Massey said the instrument just exhibited is undoubtedly a novelty as regards the question of providing for the escape of the gas In puncturing a large fibro-cyst in one case, he employed Gehrung's instrument, and was astonished at the very large quantity of gas aspirated, although a current of not over 150 to 200 milliamperes was applied for two or three minutes He thought much of the irritation ordinarily observed is due to the use of inflexible instruments About a year after the description of Dr Gehrung's instrument was published in his book, he learned from Dr Goelet that he had devised a similar instrument in ignorance of Dr Gehrung's work

Dr Dickson thought it would be better to have the tip of the instrument protected when used with strong currents He also thought the folds of mucous membrane might catch in the grooves of the spiral and lead to hemorrhage, and that when the positive pole was used, the withdrawal of the instrument might be attended with much difficulty The cleaning of the instrument after certain cases could hardly be effected by anything short of passing it through a flame

Dr Massey remarked that this instrument was an improvement on his, only in having a hollow handle

Dr. Gehrung said that without intending to advocate the puncturing method in the treatment of fibroids, he desired to mention that one of the great advantages of the instrument to which he had alluded was that it could be left in *situ* and electrolysis repeated without resorting to another puncture He also made use of the stylette by which the instrument could be introduced or withdrawn

The President remarked that it had been claimed that much of the good effect of electrical treatment is due to the action of the liberated gases If this be so why should instruments be devised to allow its escape?

Dr Hayes, in closing the discussion, said that about eighteen or nineteen years ago he had constructed an instrument which would allow of the escape of gas, but he had not published it The introduction of his instrument is not nearly so difficult as one might suppose although of course it is not so easily effected as with the ordinary instruments The tip can be readily coated with shellac, but if the electrode be introduced and allowed to remain stationary, there is very little danger in having the tip made of solid metal Even though the positive pole be used, there is no great difficulty in removing the instrument, the operation being facilitated by gently rotating it The evolution of gas is so great when strong currents are used as to prevent in a measure the adherence of the tissues to the electrode

W B Sprague, M D, of Detroit read a paper on

A CONTRIBUTION TO THE ELECTRO-THERAPEUSIS OF SALPINGITIS

The pathology of tubal troubles has been so recently evolved that the therapeusis is still in the embryonic stage Many of our leading lights declare that there can be no rational therapeusis—that there can be no remedy but extirpation—as if decapitation were a cure for cephalalgia!

Yet many men have a firmer faith in Nature's economy, and are seeking to aid her efforts at repair by, at least so far as possible, removing the cause Nearly all cases are accompanied by and most of them caused by endometritis, either acute or chronic, specific or non specific Since this has been established our first duty is plainly to relieve the endometritis To this end many forms of treatment have been advised, but Polk's revival of Sims' conception of depletion and drainage seems to be the only one which has brought satisfactory results, and the relation of parts is such that the application of this principle to the womb produces a direct as well as an indirect influence upon the tubes—it removes the cause and relieves the chronic congestion in those cases which bear the treatment well

Now the severity of the measure by which it is accomplished as taught by its author and the profession at large, has limited its applicability in the hands of even its warmest advocates Divulsion, and curetting of an inflamed womb with inflamed adnexæ has often aggravated the inflammation, making extirpation necessary This has seemed to the surgeon good ground for the argument that extirpation should be the first and only resort

But Apostoli has taught us that the same results may be attained by a milder and more rational means The intra-uterine application of the negative pole of the constant current of electricity is the most reliable method we have for treating endometritis to day, the rationale of which is this same principle of depletion and drainage, by the cataphoretic action of the current, aided by the trophic influence and by its caustic action Goelet has shown that the influence extends to salpingitis and, if carefully and judiciously used, is the safest and best treatment yet advocated for this affection He says that many cases of simple inflammation of the lining membrane of the tubes will subside with the endometritis, if free drainage through the uterine canal is established and maintained, and if protection is afforded against such influences as would tend to irritate the sexual organs

My experience leads me to indorse the foregoing most heartily, but the object of this contribution is to call attention to a modification of Goelet's treatment which has been quite successful, in a few cases, in my hands, by reporting some illustrative cases At the Michigan State Medical Society meeting held at Grand Rapids in 1890, I reported a case as follows

"Mrs H, aged 32, has had one miscarriage but for several years previously she had suffered from a pain in the right iliac region, at frequent intervals A year ago last April she began to suffer more than ever before, and she came to me for relief She told me, in describing her symptoms, that she had an enlargement in the side with pain I found this enlargement to be considerable but the abdominal muscles were strong and I could not distinctly outline it I diagnosed an ovarian tumor, and felt that my diagnosis was confirmed as I watched its growth in after days But one day she came to tell me that she had had a free discharge of yellow matter after a sensation as of something giving way the night before, and the swelling was subsiding. An examination proved the correctness of her statement, and I changed my diagnosis to pyosalpinx My treatment to this time had been merely palliative, principally faradism, to relieve the pain She was now comfortable and I suspended treatment a few weeks, when the tube began to fill again I resumed the faradism, and soon after added galvanism On June 15 I gave twenty-five milliampères, intra-uterine, negative After three intra uterine applications, the last one sixty-five milliampères, I changed to the vaginal electrode, placed against the tube, sixty five milliampères June 29 Soon after this there was a second discharge of pus, and relief from pain I gave twenty one more applications similar to the last described, before March 29, 1890, when the tube had again filled, and was giving considerable trouble I now determined to try to effect an entrance into the tube I therefore converted my graduated uterine sound into an electrode, insulating it with small rubber tubing, and passed it into the womb I then connected it with the negative pole of the battery, and turned on ten milliampères Turning the end of my sound toward the right cornu, I exerted gentle pressure against the point that I thought to be the proximal end of the tube Suddenly within five minutes, my sound slipped onward about an inch I was startled, and thought of perforation of the uterine wall, but perceiving my patient undisturbed, I decided that I had really been more fortunate than I had expected and accomplished my purpose So I passed the electrode still further in and raised the current to twenty-five milliampères for seven minutes There was free discharge of pus for several days following and renewed relief from all the symptoms I have since introduced the sound into the tube on May 12 and 25, and on June 12, the last time in the presence of Dr. Manton who kindly came in to confirm my diagnosis The tube seemed quite empty of pus at the last sitting The sound has passed more readily at each subsequent sitting, and enters to a depth of more than five inches The patient, who is a seamstress, has not lost an hour's work from treatment, and her general health is much better than a year ago" (*Trans Michigan State Medical Society*, 1890)

I administered two or three treatments to this patient soon after the above report, and have been agreeably surprised to find that she is completely cured There has not been a drop of pus discharged since, nor has there been any trouble with the uterus or adnexæ Except for a chronic pharyngitis the patient's health is perfect and she pursues her avocation without interruption

Another interesting case of pyosalpinx is as follows

In the spring of 1889 I was called to a case of acute gon-

orrhea in the person of Mrs D, aged 33 years The result was what is ordinarily called a cure, without any apparent involvement of the uterus or adnexæ at the time The uterus had been badly lacerated at a previous confinement and trachelorrhaphy was performed a little later In a short time the menstrual flow became scant and painful, and there was enlargement of the tubes, followed in a few days by a free discharge of pus and relief to pelvic distress and headache which she had suffered In the summer of 1890, the distress at the periods growing monthly more severe and prolonged, I began intra-uterine applications of galvanism, and found one day that I could pass my electrode into both tubes by a manipulation which I will describe later I have continued this treatment since at intervals varying from three days to four months, the longer intervals being later After every treatment (which is applied only when the patient is suffering from distension of the tubes), there is discharge of pus and relief to all the symptoms For the past twenty-two months I have made only twenty six applications, only five of which were given during the present year, 1893, and my patient is able to do her own housework and wait upon an invalid husband, suffering only occasional serious discomfort, whereas she had at first been able to do very little and suffered much of the time

In 1891 I reported a case of hematosalpinx before the above mentioned Society The case was as follows

Miss C aged 30 years a seamstress by occupation, had undergone a not unusual history of retroversion, endometritis, prolapse of the ovaries and salpingitis previous to the summer of 1890 She spent this summer on the New England coast and was much improved in general health when she returned to Detroit in the autumn But the menses became scant and irregular and began to usher in a very severe headache and backache which were very slow in subsiding after the menses ceased These phenomena developed with increasing severity and regularity, and I was called to see her suffering in an unusually severe recurrence, Jan 27, 1891 I found a retroversion and enlargement of the womb with an abnormal swelling in the left vaginal fornix I replaced the womb and gave internal remedies which afforded very little relief, but the headache, backache and swelling in the fornix subsided coincidently during the following several days She came to my office by my request on February 5, 22 and 25, and I made intra-uterine applications *a la* Apostoli for the endometritis On the last named date I made the following notes Left tube distended, probably by catarrhal secretions Has had much vertical headache for the past week, and a sensation of water trickling over her forehead I seemed to succeed in passing the electrode into the distended tube—at least it passed about four inches beyond the os by turning it to the left side and gave pain in the region of the left ovary Gave twenty-five milliampères negative current for ten minutes On March 1 she returned and I again noted as follows She reports that her headache was relieved soon after last treatment, and that she discharged a brown viscid material from the vagina for two days following I find the distension nearly gone from the tube and have again passed the electrode into it, beyond question, feeling its point through the abdominal wall near the ovary I gave twenty milliampères ten minutes, negative current My diagnosis now changed from that of hydrosalpinx to hematosalpinx, but I determined to try what a persistence in this line of treatment might do for her On March 16 I again recorded I repeated the intra-tubal treatment March 9, but did not succeed in entering the tube so far This treatment was followed by menses next day, which were free from pain, normal in quantity, and followed by no headache She reported these facts yesterday, March 15, when I gave another treatment, introducing the electrode probably more than an inch into the tube She says she is "perfectly well"

I repeated the treatments twice more in March and her menses recurred April 4 quite normal and freer than formerly She reported another menstrual period ushered in May 30 which was the most normal in all respects that she had experienced for many months I continued to maintain the patency of the tube by occasional treatments for a few months and there has never been a recurrence of the hematosalpinx I reported the case in June of the same year, when I wrote as follows "My patient is very comfortable unless she runs a sewing-machine or takes a long walk, in spite of the abnormalities in her pelvis From my experience in treatment, by electrolysis, of stenosis of the cervical canal, I expect to obtain a permanently patent uterine orifice in the diseased tube, and to have cured my hematosalpinx" This patient was married the following spring and on July 14, 1892, I was called in haste, but too late to prevent the loss of a two months fetus, due to a recurrence of the retroversion which she had endured for several days without reporting Her menses again ceased March 1 of the present year and on the 26th of July she felt motion By careful watching the womb was kept in position until the danger of abortion was passed

During the discussion which followed the report of this case in 1891, I took occasion to argue for greater conservatism in these cases, in answer to which Detroit's leading extirpationist spoke as follows

"I don't know how many children Dr Sprague's patient has, or how many she will get in the future I think she is unsexed I think her generative organs, as far as propagation of species is concerned, are of no more use to her, and I believe with Dr Manton, that very serious irritation is likely to take place and subject her to great danger in the future" (*Trans Mich State Med Soc 1891*)

Thus, incidentally, the case has developed an unanswerable reply to the plea for immediate extirpation in such cases

I have not been able to find that any one else has advocated seriously or practiced intra-tubal electrolysis for any form of salpingitis I am aware that the possibility of entering the tubes in these cases is discredited, and I have found many cases in which I have been balked in my efforts, but I have good reason to believe that I have succeeded in several cases besides these that I have reported, and I have had no untoward results following my efforts in any instance Even where I am convinced that I failed, I have frequently given great relief to the patient and sometimes caused free discharge of catarrhal or purulent secretion, as the case might be It seemed to me, therefore, that after three years of careful effort and observation in this direction it was desirable to lay the matter before this, the only body of men in our country competent to pass upon and approve or condemn a continuation of effort in the same line

I have believed that the number of cases in which we could apply the treatment is necessarily limited, but that in many cases, where it is possible, the direct application of the current to the diseased membrane would be far more beneficial than to depend upon the remote and secondary effects of applying it to the endometrium I do not ignore the danger of careless manipulation in this region, and most earnestly warn tyros in electro-therapy from making the attempt to enter the tubes with any electrode The strictest asepsis should be observed before, during and after the séance

I use an insulated Simpson sound with the normal curve a little accentuated at the extremity As soon as I have passed the internal os uteri, I turn the point of the instrument to the side which I wish to enter and gently follow along the bottom of the fossa until I reach the os uterinum of the tube, which is indicated by the points sliding into a slight depression I then attach the negative conductor, turning on slowly, ten to thirty milliampères, according to the nature of the case I exert just sufficient leverage to hold the bulbous point in firm contact with the ostium I usually notice evidence of the cataphoretic action by oozing of fluid from the os uteri In those cases where I have succeeded in entering the tube, I have felt the point of the electrode suddenly advance, and have immediately found it fixed, as if in a narrow canal In some instances I have then been able to advance it from one to two inches farther, and then have felt the point in the ovarian region, with the other hand, through the abdominal wall, in several instances After the first one or more treatments, the point does not always stop at the fornix, but enters the tube readily, as was the case in the instance where Dr Manton verified my observations I have always exercised great care to avoid force, simply guiding the electrode, with my hand supported at the forearm With this precaution, and the low current used, I do not think the danger of perforation is as great as is sometimes represented

(*To be continued*)

Philadelphia Pathological Society—The semi-annual conversational meeting of the Philadelphia Pathological Society will be held in the upper hall of the College of Physicians Building, Thirteenth and Locust Streets, on Thursday, April 26, 1894, at 8 P M Dr Simon Flexner, Associate in Pathology in the Johns Hopkins Medical School, will deliver an address entitled, "An Experimental Study of the Nature and Action of Certain So called Toxalbumins" Members of the medical profession are cordially invited to be present

THE
Journal of the American Medical Association
PUBLISHED WEEKLY

SUBSCRIPTION PRICE, INCLUDING POSTAGE
PER ANNUM, IN ADVANCE $5 00
SINGLE COPIES 10 CENTS

Subscriptions may begin at any time and be sent to
THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION,
No 68 WABASH AVE CHICAGO ILLINOIS
F J REBMAN LONDON AGENT 11 Adam Street STRAND LONDON
W H LOWDERMILK & CO WASHINGTON AGENTS

MEMBERSHIP IN THE AMERICAN MEDICAL ASSOCIATION

This is obtainable, at any time by a member of any State or local Medical Society which is entitled to send delegates to the Association All that is necessary is for the applicant to write to the Treasurer of the Association Dr Richard J Dunglison, Lock Box 1274 Philadelphia, Pa, sending him a certificate or statement that he is in good standing in his own Society, signed by the President and Secretary of said Society, with five dollars for annual dues and subscription for THE JOURNAL. Attendance as a delegate at an annual meeting of the Association is not necessary to obtain membership On receipt of the above amount the weekly JOURNAL of the Association will be forwarded regularly

All members of the Association should send their Annual Dues to the Treasurer, RICHARD J DUNGLISON M D., Lock Box 1274 Philadelphia Pa

SATURDAY, APRIL 7, 1894

THE DEPARTMENT OF PUBLIC HEALTH

The AMERICAN MEDICAL ASSOCIATION four years ago set about the task of securing at the hands of Congress a Department of Public Health, and the committee appointed for that work has been steadily at work Much has been done to clear the way to united action, and but for the hasty and ill-judged action of the New York Academy of Medicine, the matter would already be far advanced That the bill proposed by that body to establish a "Bureau" of Public Health, was singularly defective they now admit, and have withdrawn the original bill providing for sanitary districts and have substituted a much better one It is, however, far inferior to the broad plan of a Department of Public Health

The bill of the AMERICAN MEDICAL ASSOCIATION Committee, contents itself by forming the Department, and leaves the details of subsequent organization and development to the Department itself It is not reasonable to suppose that Congress will ever create such a Department unless it means to be guided somewhat by its advice in rendering its work effective, so then at present there is only one thing to do, and that is to work earnestly to secure the passage of the AMERICAN MEDICAL ASSOCIATION bill, which we understand will be introduced in the Senate by the Honorable JOHN SHERMAN, of Ohio, and in the House by the Honorable JAMES B MCCREARY, of Kentucky

We earnestly hope that the New York Academy of Medicine will cease to urge its "Bureau" scheme against the great measure now proposed by the ASSOCIATION

It is said that the reason for holding back is that there is immediate probability of its passage, for certain very distinguished persons in authority are against another Cabinet office In other words our legal brethren are so well entrenched in what they now seem to regard as a right inherent in their profession, that the welfare of the country forms no part of the argument

We know we are right in making this request for a substantial recognition of our profession A first class sanitarian in the Cabinet would be one of its most useful members, let us therefore make no halt in our efforts toward securing this result Our ASSOCIATION reaches every Congressional district, let every member write to his member of Congress and ask *his unqualified support* of the AMERICAN MEDICAL ASSOCIATION bill, "to establish a Department of Public Health," and to oppose any bill having for its purpose the establishment of any alleged "Bureau of Health"

It may not and very likely can not be passed at this session, but let us make the attempt, and if we fail, let us obtain from the candidates who will be *nominated* for Congress during the coming summer, a categorical and definite answer to the question, Will you, if elected, favor the bill to create a Department of Public Health? Let us put this question to every candidate this summer and we will have some definite result from the next Congress In a free country with ballots in our hands, we are not helpless if we make organized effort Medical societies in affiliation with the AMERICAN MEDICAL ASSOCIATION, and those in sympathy with the movement should lose no time in passing resolutions favoring the establishment of a Department of Public Health, and copies of these resolutions should be forwarded by the secretary of the society to the members of Congress from the district in which the society is located

The petition framed by the committee, which was published last week, while rather lengthy, furnishes in proper form the most cogent reasons for the passage of the bill The prevention of disease, the amelioration of suffering, the improvement of the condition of the poor, and the lengthening of human life are objects sought to be attained by the proper utilization of the powers and forces of our Government To this beneficent and patriotic work our noble ASSOCIATION joining the American Public Health Association, has set its hand, *and let us see to it* that when we ask for this great establishment we are not given a petty Bureau

Let us also insist that whoever of our profession shall be entrusted with this great work, after the formation of the Department, shall be clothed with such rank as shall make his office equal in dignity to those held by the members of the legal profession

THE ASSOCIATION TRAIN

We respectfully urge upon members who intend going to San Francisco to concentrate on the Association Train wherever possible, by that means we

raie, d'origine embryonnaire, par le traitement par le méthotrexate Une autre est l'application de la cytologie exfoliative pour mettre en évidence un cancer précoce du col de l'uterus Dans une autre étude récente, on fit passer en série le virus Coxsackie B3 plusieurs fois à travers des tumeurs humaines développées chez les rats, et il fut ainsi "entraîné" à détruire ces *tumeurs*

Une autre découverte est l'observation d'un rapport possible entre les facteurs concernant l'infection et le cancer Des études sur les propriétés des sucres complexes, à poids moléculaire élevé, connus sous le terme de polysaccharides, montrèrent qu'ils produisent chez les animaux de laboratoire non seulement des réactions caractéristiques des infections bactériennes, *mais aussi des manifestations tumorales*

On est en train d'étudier intensivement le cancer du poumon, dans des voies diverses, pour combattre l'augmentation en flèche de ce type de cancer qui survient particulièrement chez les hommes âgés de plus de 45 ans Des études épidémiologiques ont établi une association statistique entre la fumée de cigarette et le cancer pulmonaire Egalement des études sont en cours pour améliorer les moyens de diagnostic et de thérapeutique, destinés à raccourcir l'intervalle entre l'apparition de l'affection et le traitement, et pour augmenter l'efficacité du traitement

Le grand nombre des succès illustre amplement la valeur de la coopération dans la recherche du cancer En fait, ce n'est pas une science en elle-même, mais l'activité simultanée de beaucoup de disciplines scientifiques indépendantes

ZUSAMMENFASSUNG

Einige wichtige Gebiete der Krebsforschung, die die Fortschritte der Zukunft bilden konnen, sind die Chemotherapie, Cytologie, Virusforschung und Immunologie Die kurzlichen Fortschritte auf diesen Gebieten werden anschaulich gemacht durch eine Vielzahl von Leistungen

Eine von diesen ist die Hemmung des Chorion-Carcinomas, eines seltenen, soliden, bosartigen Tumors, embryonalen Ursprungs durch Behandlung mit Methotrexat Eine andere ist die Anwendung der Cytologie abgestossener Ephitelien zur Entdeckung eines fruheren Gebarmutterhalskrebses In der kurzlich erfolgten Erreichung eines anderen Zieles liess man das Coxsackie-B3-Virus periodisch nemrere Male durch bei Ratten wachsende menschliche Tumoren passieren und "Trainierte" sie so, diese Tumoren bei den Ratten zu zerstoren

Ein anderer Befund ist die Beobachtung einer moglichen Beziehung zwischen den bei der Infektion und dem Krebs beteiligten *Faktoren* Studien uber die Eigenschaften der complexen Zuckerverbindungen von hohem Molekular-Gewicht, die als Polysaccharide bekannt sind, ergab, dass sie bei Laboratoriumstieren nicht nur Reaktion entwickelten, die charakteristisch waren fur infektiose Bakterien, sondern auch den Tumor schadigten Intensive Untersuchungen uber den Lungenkrebs sind auf einer Vielzahl von Wegen im Gange mit dem Bemuhen, den steilen Anstieg dieser Krebsart zu bekampfen, der sich besonders bei Mannern

uber 45 Jahren ereignet hat Epidemiologische Untersuchungen haben ein statistische Beziehung begrundet zwischen dem Zigarettenrauchen und dem Lungenkrebs Ausserdem sind Untersuchungen im Gang zur Verbesserung der diagnostischen und therapeutischen Massnahmen mit dem Ziel, den Zeitabstand zu verkurzen zwischen dem Beginn und der Behandlung der Krankheit, und um die Behandlung wirksamer zu gestalten

Die Vielzahl von Leistungen veranschaulicht zur Genuge die cooperative Natur der Krebsforschung Sie ist in der Tat keine Wissenschaft fur sich allein, sondern besteht aus der Tatigkeit vieler fur sich bestehender wissenschaftlicher Disziplinen

BIBLIOGRAPHY

Guthrie, D *A History of Medicine*, J P Lippincott Co, Philadelphia V, 1946

Endicott, K M, Leiter, J, Shimkin, M B and Huttrer, C P "The Cancer Chemotherapy National Service Center—A National Voluntary Effort," *Proc Am Assoc for Cancer Research*, 2 199, 1957

Farber, S, Toch, R, Sears, E M and Pinkel, D "Advances in Chemotherapy of Cancer in Man," *Advances in Cancer Research*, 4 1, 1956

Li, M C, Spencer, D B, Hertz, R and Lubs, H A "Suppression of Trophoblastic Tumors in Man by Antifolic and Antipurine Compounds," *Proc Am Assoc for Cancer Research*, 2 226, 1957

Erikson, C C, Everett, B E, Graves, L M, Kaiser, R F, et al "Population Screening for Uterine Cancer by Vaginal Cytology," *J A M A*, 162 167, 1956

Tolles, W E "The Detection of Malignant Cells in Cytologic Material by Electronic Means—the Cytoanalyzer" Proc of the Third Natl Cancer Conference, Detroit, Mich J P Lippincott Co, Philadelphia 636-643, 1957

Stanley, W M "The Virus Etiology of Cancer" Proc of the Third Natl Cancer Conference, Detroit, Mich J P Lippincott Co, Philadelphia 42-51, 1957

Suskind, R G, Huebner, R J, Rowe, W P and Love, R "Viral Agents Oncolytic for Human Tumors in Heterologous Host, Oncolytic Effect of Coxsackie B Viruses," *Proc Soc Exper Biol and Med*, 94 309, 1957

Love, R, Suskind, R G and Huebner, R J "Mechanism of Oncolysis Produced in HeLa Cells Grown in Cortisonized, Irradiated Rats by Infection with Coxsackie B_3 Virus," *Proc Am. Assoc for Cancer Research*, 2 227, 1957

Landy, M and Shear, M J "Host Responses Elicited by Polysaccharides of Bacterial and Mammalian Derivation" Presented at Meeting of Federation of *Am Soc for Experimental Biology*, Chicago, April 1957 *Fed Proc*, 16 564, 1957

Friend, C "Immunological Studies on a Filterable Agent Causing Leukemia-like Disease in Mice," *Proc Am Assoc for Cancer Research*, 2 204, 1957

Griswold, M H, Wilder, C S, Cutler, S J and Pollack, E S *Cancer in Connecticut* Connecticut State Dept of Health, Hartford 141, 1955

Cutler, S J and Loveland, D B "The Risk of Developing Lung Cancer and Its Relationship to Smoking," *J Natl Cancer Institute*, 15 201, 1954

Dorn, H F and Cutler, S J "Morbidity from Cancer in the U S Part 1, Variation in Incidence by Age, Sex, Race, Marital Status, and Geographic Region," *Public Health Monograph*, 29 1, 1955

Cutler, S J "A Review of the Statistical Evidence on the Association Between Smoking and Lung Cancer," *J Am Statistical Assoc*, 50 267, 1955

Horn, D *Trends in Lung Cancer Statistics* Proc Third Natl Cancer Conference, Detroit, Mich 1956 J P Lippincott Co, Philadelphia 457-461, 1957

Heller, J R "Lung Cancer," *J Chronic Dis*, 1 96, 1955

Stocks, P and Campbell, J M "Lung Cancer Death Rates Among Non-smokers and Pipe and Cigarette Smokers," *Brit M J*, 2 923, 1955

Wynder, E L, Bross, E J, Cornfield, J and O'Donnell, W E "Lung Cancer in Women," *New England J Med*, 225 1111, 1956

Doll, R and Hill, U B "Lung Cancer and Other Causes of Death in Relation to Smoking A Second Report on the Mortality of British Doctors," *Brit M J*, 2 1071, 1956

Hammond, E C "Etiology of Bronchogenic Carcinoma," Cancer Abstract—*Bulletin Cancer Progress*, 6 156, 163, 1956

Stowell, R E *Exfoliative Cytology in the Diagnosis of Lung Cancer* Proc Third Natl Cancer Conference, Detroit, Mich 1956 J P Lippincott Co, Philadelphia 508-513, 1957

Tuddenham, W J *The Roentgen Diagnosis of Carcinoma of the Lung* Proc Third Natl Cancer Conference, Detroit, Mich 1956 J P Lippincott Co, Philadelphia 526-528, 1957

Guttmann, R J "Two Million Volt Irradiation Therapy for Inoperable Carcinoma of the Lung," *Cancer*, 8 1254, 1955

Shryock, R H *The Development of Modern Medicine* Alfred A Knopf, New York 457, 1957

What Are the Facts About Cancer? What Are We Doing About Cancer? Natl Health Education Committee, Inc New York 1-27, 1957

Clinical and Biological Investigations on the New Antituberculosis Drugs (Pyrazinamide and Cycloserine)

A OMODEI ZORINI, M D , F C C P ,* G SPINA, M D ** and G E De SIMONI, M D **
Rome, Italy

Pyrazinamide

Up to now at the Carlo Forlanini Institute, about 100 patients have been treated with pyrazinamide † Here we will report only a first group of 30 patients having undergone a whole regimen of therapy (four to six months), and for whom a number of biological tests were carried out that will be reported elsewhere

The above mentioned 30 patients (15 men and 15 women) were affected by various forms of pulmonary tuberculosis, of which 11 were moderately advanced (one essentially exudative, ten essentially productive) and 19 chronic (six essentially exudative, two with residual cavitation, one tuberculoma) Of these chronic forms, four (two productive, two exudative) showed some exacerbation phenomena at the start of pyrazinamide therapy

All patients had already received prior therapy with other antibiotics and antituberculosis chemotherapeutic agents, and most of them had presented tubercle bacilli in sputum more or less resistant to streptomycin, isoniazid and PAS Except for some cases without clinical findings, the objective auscultatory findings of the lungs were quite prominent Patients were carefully selected so as to eliminate any that had evidence of hepatic dysfunction The daily dose of the drug (divided into five times a day) was 2 5 gr gradually reached at the fourth day of treatment In addition to routine roentgenographic, planigraphic and laboratory examinations (B U N , F B S , urine, and sputum analyses), repeated controls were carried out These were related to the peripheral blood count, serum electrophoresis, the phagocytosis index, Middlebrook-Dubos test, P B I urinary 17-ketosteroids, behavior of the specific proteases, serum lipase power, serum cholesterol, serum bilirubin, plasma fibrinogen, prothrombin time, colloidal serolability tests, hippuric acid and B S P tests

In Table I the important clinical roentgenographic and laboratory results are summarized, before and after 80 days of therapy

The drug tolerance in the doses we used was generally good, except for appearance of arthralgic phenomena in three patients, in one, symptoms started after a few days' treatment and were present in the articulations of the upper and lower members, but without tumefaction It is to be noted that such arthralgic phenomena completely disappeared with

*Director, Carlo Forlanini Institute
**Assistants at the Carlo Forlanini Institute
†The reported data correspond to the first of December, 1956

the temporary suspension of therapy In another patient, therapy was restarted after a 20-day interval A clinical picture of acute hypoadrenal corticalism was noted, featured by severe asthenia, marked hypotension, dyspepsia, generalized hyper-pigmentation, marked decrease of the urinary 17- ketosteroids, and by an alteration of serum electrolytes, principally saline

In regard to the incidence of hepatic disturbances as outlined in the literature, we observed one case with abnormal bromsuphalein retention In two other patients, jaundice with high fever was noted at the 42nd and at the 90th day of therapy, after some early symptoms of asthenia, anorexia, and dyspepsia In both cases, the pyrazinamide administration was stopped Furthermore, in two other patients, one could observe the temporary formation of edema and in a third one, an urticaria of short duration A pertinent observation, limited to the female patients, is the manifestation of brown pigmentation of the skin of the body exposed to the light (face, neck, hands), this phenomenon slowly regressed after the cessation of therapy

In view of the absence of any evidence of hypo-adrenal corticalism as determined by our tests, and in consideration that the pigmentation was limited to the skin exposed to the sun, this phenomenon has been interpreted by us as an increase of the photo-sensitivity of the skin It could be possible that a metabolic alteration of vitamin PP was also a factor

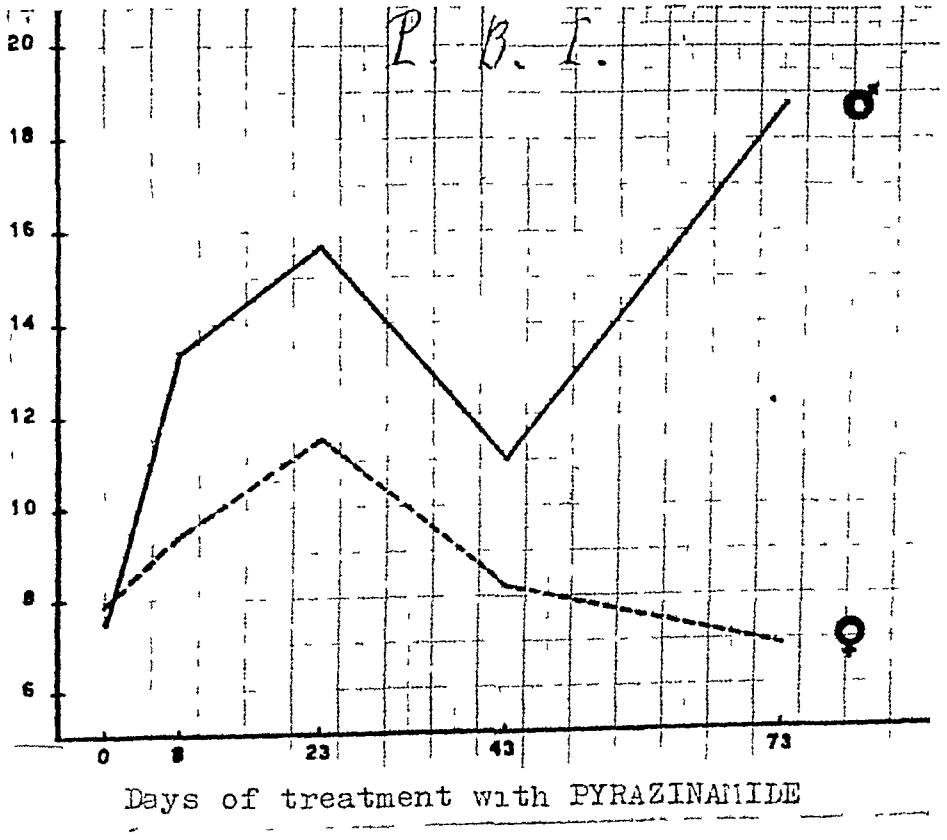


FIGURE 1

TABLE I

Clinical and Laboratory Data	Prior to Pyrazinamide Treatment		Number of Cases	After Pyrazinamide Treatment	Number of Cases
General conditions (cenesthesia, forces appetite, dynamism, toxiemic status)	Good		11	Improved	20
	Mediocre		8	Unchanged	6
	Decayed		11	Worse	4
Local conditions — Clinical Report				Temporarily improved	2
				Improved	10
				Unchanged	15
				Worse	3
Local conditions — RX				Transiently improved	3
				Improved	7
				Unchanged	13
				Worse	7
				Cavity regression (included in improved subjects)	3
Fever temperature	Present		8	Appeared	2
	Absent		22	Disappeared	3
				Temporarily disappeared	2
				Decreased	0
				Unchanged	23
Coughing and expectoration	Positive	direct	69,23%	Increased	5
		on culture	58,83%	Unchanged	8
				Decreased	10
Tubercle bacilli research in the expectoration	Negative	direct	30,76%	Disappeared	7
		on culture	41,17%	Haemophtisis of slight entity	2
				Positive — direct	61,53%
				Positive — on culture	58,83%
				Negative — direct	38,47%
				Negative — on culture	41,17%
Weight				Increased	15
				Unchanged	6
				Decreased	9
S R				Increased	12
				Unchanged	6
				Decreased	12
Toxic phenomena				Artralgia	3
				Jaundice	2
				Urticaria	1
				Asthenia	?
				Dispeptic troubles	5
				Oedema appearance	2
				Hyperpigmentation of uncovered sides to light	12
Glycemia				Meaning-less oscillations	
Azotemia				Did not show particular variations as for starting values	
Urinary findings				Albuminaria increase in 30% of cases, appearance of urobilinuria in 5 cases, of biliary pigments in 3 cases and of haematuria in 4 cases	

In the course of the clinical experiment, a number of biologic investigations were carried out, the results of which are presented in the following summary

1) *The precipitable bound iodine* elevated until the 23rd day of therapy (higher in males than in females) and after a short decrease from the 43rd day, it demonstrated a dissociated behavior in the two sexes, in the sense of a marked increase for the males and of a further reduction for the females (Figure 1)

2) *The serum cholesterol and cholesterol-esters,* after a slight fluctuation within the the first week, serum levels returned almost to the initial values, remaining like that until the end of the observation period (Figure 2)

3) *The serum proteins* were notably influenced by the drug, *the total proteins* had remained stable at or near the initial value, until the 43rd day, following which a sudden marked decrease was noted *Albumin* showed a tendency to increase until the 43rd day, and thereafter, like the total proteins, they underwent a marked decrease The mean values of the *total globulin* consistently decreased until the 73rd day, consequently, the A/G ration, by the 43rd day, increases and tends to reach the value of 1, thereafter, it shows a tendency to decrease again As for

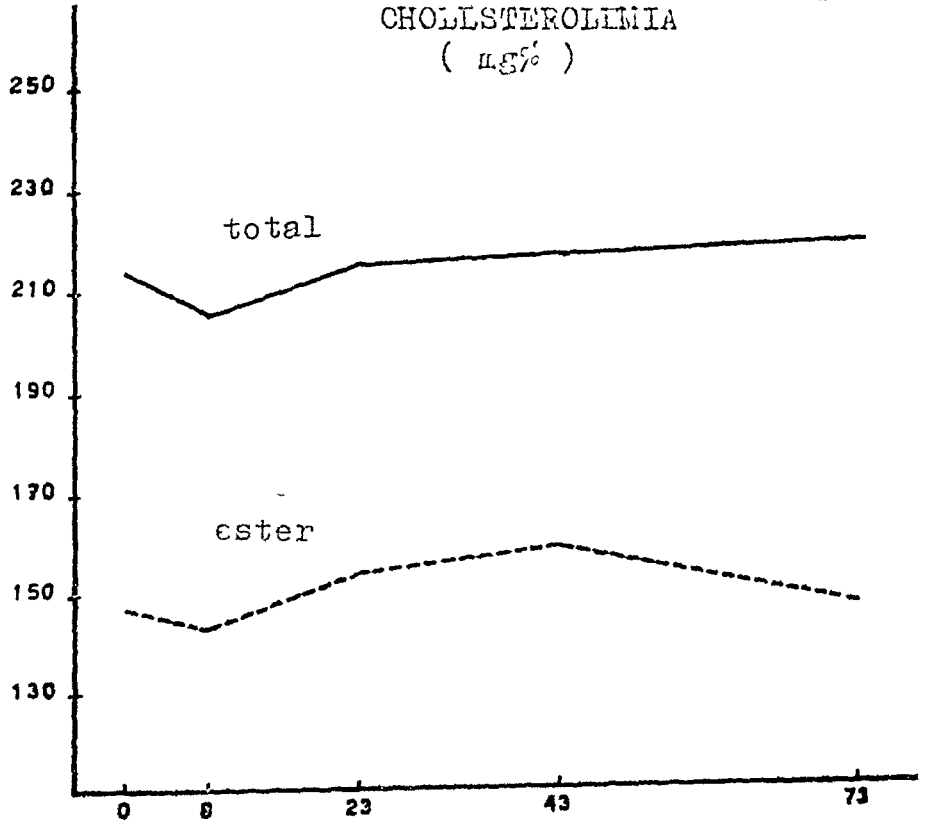


FIGURE 2

the individual *globulin fractions*, we observed that alpha 1, alpha 2 and gamma globulin tend to decrease, and beta globulin tends to increase, therefore, values in per cent of total globulin, which reveal the relations between the single globulin fractions, shows that while the decrease of alpha 1 and alpha 2 globulin has little meaning, the decrease of gamma globulin and the increase of beta globulin point out that the variations of these two fractions are more marked

The *plasma fibrinogen* is but slightly influenced until the 23rd day of therapy, thereafter, it increases rapidly, presenting at the 73rd day of treatment mean values much higher than the initial ones (Figure 3)

4) *The prothrombin time*, after a marked increase within the first week, keeps lengthening more slowly until the 73rd day, and during the entire period, values are notably increased in relation to the starting ones (Figure 4)

5) *Urine 17-ketosteroid* Within the first week of treatment, a sudden fall is noted, nearly exclusively in the male patients, and precisely for the same period wherein the increase of P B I occurs (Figure 5)

6) *The peripheral blood counts* presented slight modifications of the

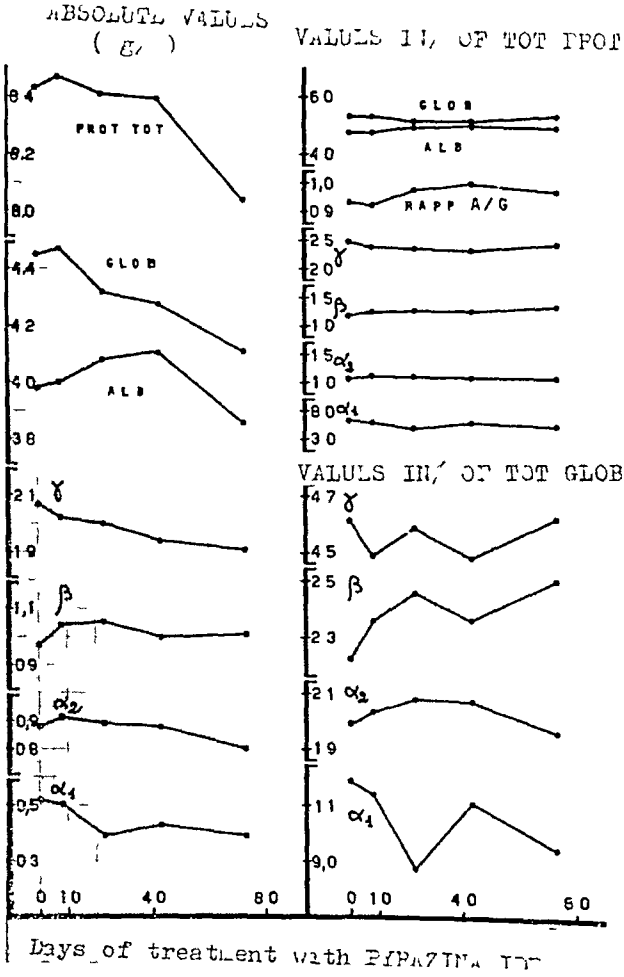


FIGURE 3

red series Platelets showed a marked tendency to decrease, reaching the minimal level at the 43rd day *The white series* presented a progressive leukopenia which, on the 73rd day, reached a mean value of 4 900 *Leukocytes* were slightly modified

7) *The plasma lipasic power* presented some initial decrease, as occurred with INH, and thereafter it tends to reach a value corresponding to the clinical result (Figure 6)

8) *Specific proteases of defence in urine* presented a frequent initial decrease, forming then a descending curve that is very similar to that obtained during INH therapy (Figure 6)

9) In 15 out of the 30 subjects, the behavior of the Middlebrook-Dubos reaction and of phagocytosis was studied, no significant derivations were noted in the former, while phagocytosis showed a progressive decrease in cases with a favorable course

The clinical and functional behavior of the liver, on the basis of our

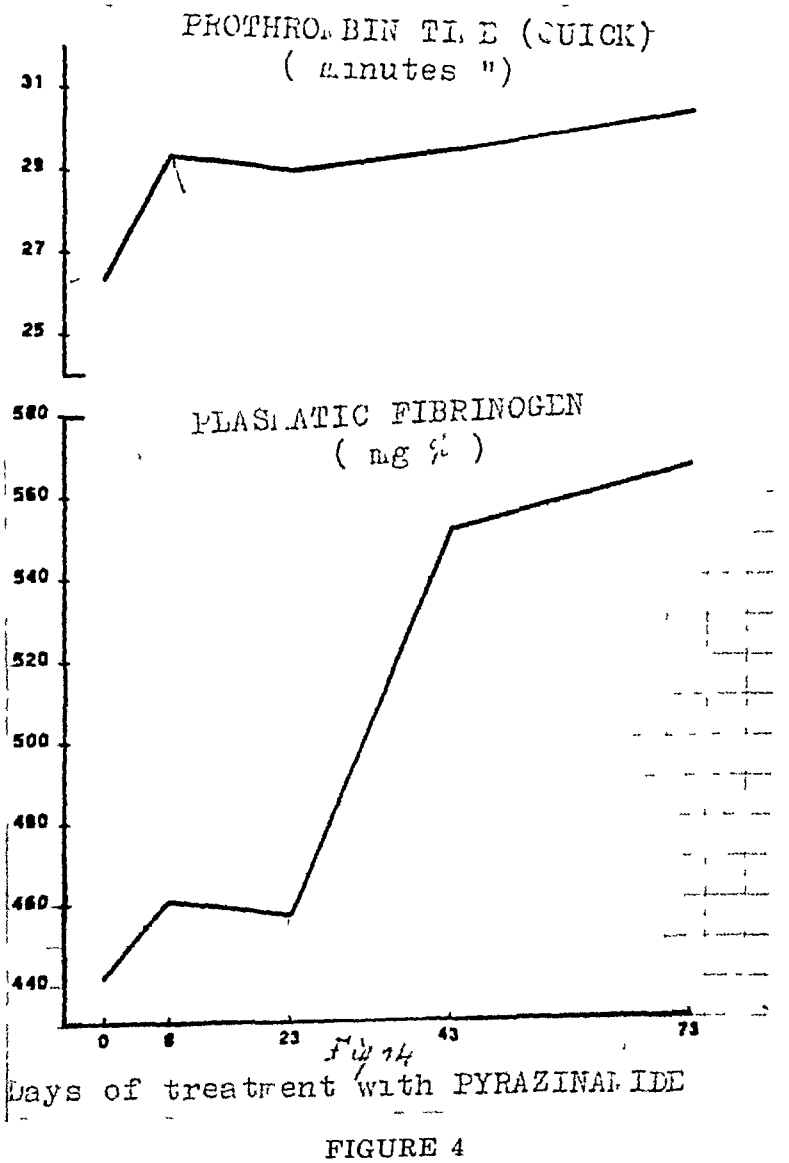


FIGURE 4

studies, showed *an exacerbation or the appearance of dyspepsia* in ⅓ of the cases, furthermore, *hepatic dysfunction is more frequently noted in subjects with preexisting hepatic disease and in those with no favorable results from therapy According to the results of the laboratory tests done for evaluation of liver function, an evident agreement with the clinical observations is noted*

In concluding, we can say that pyrazinamide therapy has resulted in subjective improvement of a good number of patients, at least for the first 40-50 days of therapy This is important when considering that many of these patients were affected by chronic disease and had failed to show satisfactory improvement on other well known chemotherapeutic

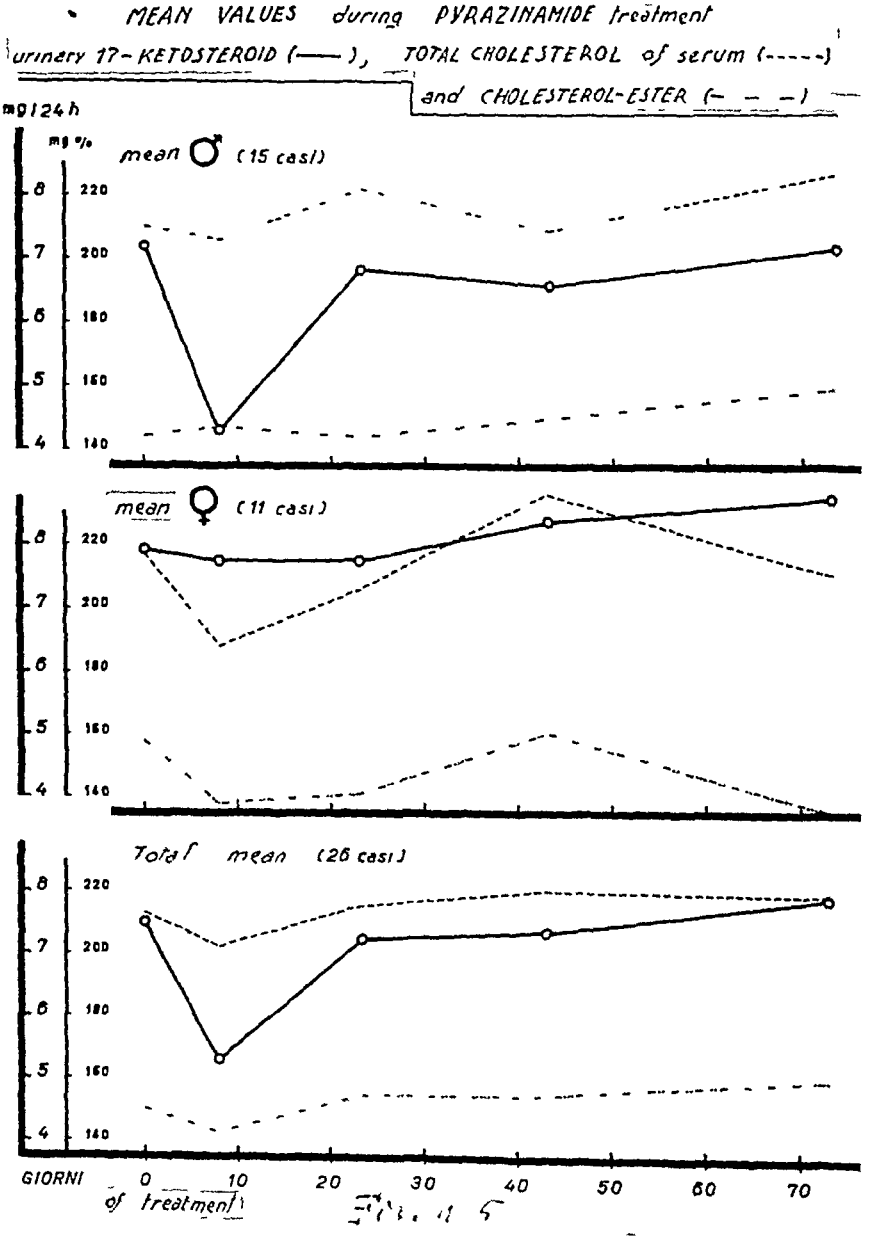


FIGURE 5

agents, because of intolerance or resistance In modification of the above, we have not always observed roentgenographic improvement corresponding to the clinical state In only seven cases were beneficial variations observed From the point of view of complicating phenomena, two cases having jaundice and arthralgic episodes (these last being only transient) have to be mentioned

In consideration of these observations, we can suggest that pyrazinamide should be utilized in the therapy of pulmonary tuberculosis only after the employment of more effective and less toxic agents, furthermore, the treatment period should not be too long (a maximum of 40-50 days) with the possibility of reinstating the administration in the interval of therapeutic regimens executed with other antituberculosis drugs We do not have sufficient experience of treatment with pyrazinamide of cases of recent pulmonary tuberculosis, as have been reported in the American literature, and in the Italian literature by Daddi It might be postulated that, in such conditions, therapy with pyrazinamide of short duration, eventually combined with isoniazid, could develop a remarkable therapeutic action, even if the toxic effects on the parenchyma of the liver are added

At the present time, however, we do not believe it worthwhile to substitute this new antituberculosis agent in the place of combined therapy

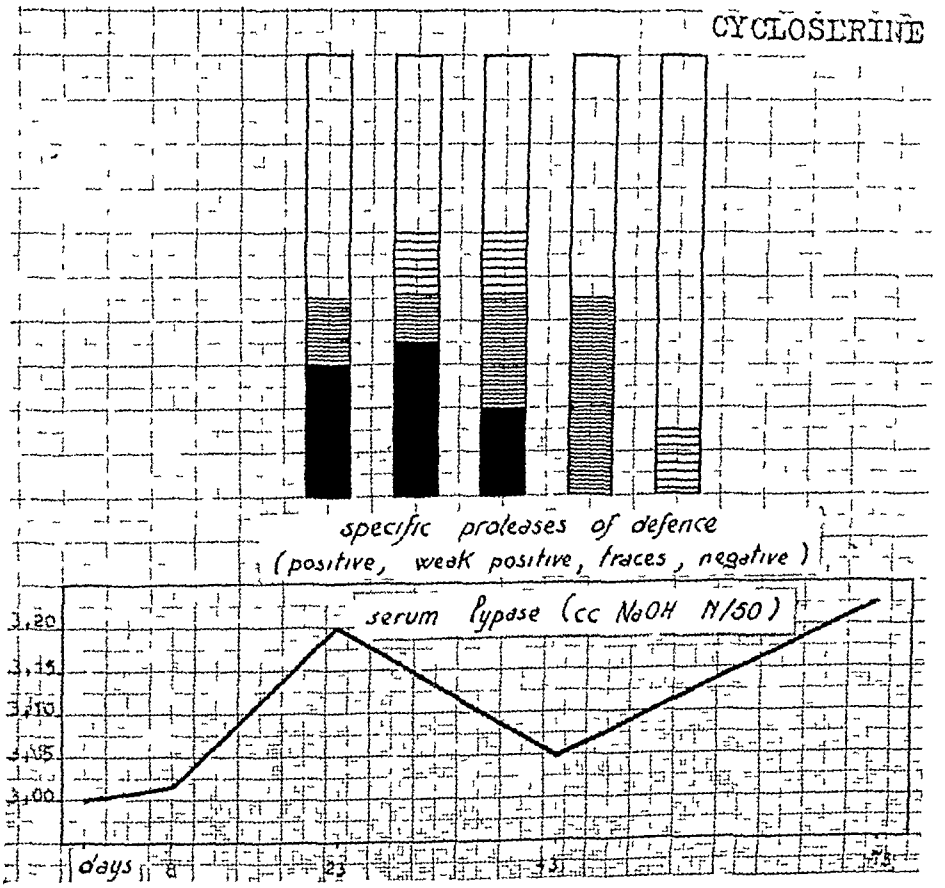


FIGURE 6

with streptomycin and isoniazid This latter, in our opinion, remains the principal therapeutic method in the treatment of the incipient active post-primary tuberculosis

Cycloserine

Our experience with this new antibiotic (supplied through the courtesy of Lilly, Merck, and Pfizer firms) is based on eight months of clinical observations on a total series of 88 patients . Sixty patients were treated with cycloserine alone (50 received a dose of 1 gr /daily, and ten 1 5 gr /daily, 26 had combined therapy of cycloserine (0 50 gr /daily) and isoniazid (300-400 mgr /daily) , one cycloserine (0 50 gr /daily) and streptomycin (1 gr /daily) and one with cycloserine (0 50 gr /daily) and PAS (6 gr /daily) In the first group of 31 patients, (see table) the drug was administered in the dose of 1 gram daily (subdivided into four equal doses) starting on the first day, while in the other groups treated, this dosage level was reached gradually

The clinical forms at the start of the therapy could be distinguished as follows eight cases of pulmonary tuberculosis of early exudative and moderately advanced types (from one to five months of clinical evolution) with the clinical picture of early lobar infiltration or localized tuberculosis Four were not treated with common anti-tuberculosis chemoantibiotics and four were treated with modest doses of streptomycin and isoniazid

Five patients with exudative pulmonary tuberculosis of recent onset, moderately advanced, presenting a picture of confluent caseous extensive bronchopneumonia

Ten cases of pulmonary tuberculosis, mainly exudative or miliary, moderately advanced, that in the course of chronic pulmonary tuberculosis or breakdown of old infiltrations or lobar disease

Two cases of chronic disseminated miliary tuberculosis (cold miliary) resistant to the common antituberculosis chemoantibiotics,

Two cases of chronic metapneumothoracic empyema, combined and fistulized

Six cases of chronic fibro-ulcerous or ulcero-caseous pulmonary tuberculosis, limited or extensive

On the whole, therefore, we have treated 23 patients presenting with disease either advanced in the primary state or that occurring secondary in the course of a chronic illness, and 65 chronic forms

The clinical and pertinent laboratory results have been collected in a table Only in the first 31 cases therapy was terminated after 15 days (one case) to five months (Table II)

A) *From the clinical point of view,* the antibiotic, during the first phase of the therapeutic regimen, induced an improvement of the cenesthesia with remarkable decrease of coughing and expectoration, where they were present, and disappearance or decrease of fever in at least two-thirds of the treated cases

For the first ten days of treatment, in about half of the cases a slight transient weight loss was observed with subsequent return to normal

TABLE II

Clinical and Laboratory Data	Prior to Cycloserine Treatment	Number of Cases	After Cycloserine Treatment	Number of Cases
General conditions (cenesthesia, forces appetite, dynamism, toxemic status)	Good	7	Improved	17
	Mediocre	13	Unchanged	10
	Decayed	11	Worse	4
Local conditions — Clinical Report			Improved	21
			Unchanged	6
			Worse	2
			Deaths	2
RX			Slightly improved	6
			Improved	15
			Unchanged	6
			Worse	4
			Cavity regression	7
Fever temperature	Present	13	Appeared	2
	Absent	18	Disappeared	8
			Decreased	3
			Unchanged (where it was absent)	11
Coughing and expectoration	Abundant	9	Increased	0
	Scarce	22	Unchanged	11
	Absent	0	Decreased or disappeared	20
Tubercle bacilli research in the expectoration	Positive direct	26		
	Positive on culture	27		
	Negative direct	5	Positive direct	13
	Negative on culture	4	Positive on culture	16
			Negative direct	18
			Negative on culture	15
Weight			Increased	19
			Unchanged	8
			Decreased	4
S R			Increased	3
			Unchanged	6
			Decreased	22
Toxic and Allergic phenomena			Urticaria eruction	2
			Transient Art Hypot	11
			Drowsiness and Adynamia (within the first week of therapy)	12
			Convulsive crises	3
			Fever reactions (within the first week of therapy)	9
Glycemia			Unchanged	
Azotemia			Unchanged	
Urinary findings			Unchanged	

Some patients gained weight, and after a seven month period of observation, this was true for 62 per cent of the cases Examination of the lungs showed a marked decrease of rales in 17 cases from the onset of therapy, in two, after one month of therapy, rales were again noted in the same site, but they were less prominent than before and shortly thereafter were not detectable on auscultation After eight months of therapy, the clinical findings were improved in 21 cases and unchanged or worsened in the others Two patients died, one after two months, the other after 27 days of therapy In both cases, a form of chronic pulmonary tuberculosis, far advanced, was present with accompanying hemoptysis

B) *The roentgenographic picture* was improved in 21 subjects (67 per cent) Evident with regression of wide exudative or miliary processes and the reduction or disappearance of pulmonary cavities in eleven cases (36 per cent) was noted

We do not know if this disappearance will be temporary or permanent because of the short time that elapsed from the cessation of therapy (one to five months) In one case, a relapse was observed, however, after the reinstitution of therapy, regression of the pulmonary lesions was observed

As for the clinical forms, we noted that the tuberculous processes, moderately advanced and severe, clinically primary or secondary in the course of a chronic pulmonary phthisis, had greater beneficial effects from the therapeutic action of the drug than did the chronic forms In fact, out of nine patients who have completed therapy, seven showed regression or clinical stabilization of the morbid process

However, in regard to the 18 cases of chronic or hyperchronic phthisis, resistant to the other antibiotics, we observed remarkable improvements with regression of old cavities in four patients Six showed improvement of a slight degree, four were unchanged, two have become worse, and two have died

In one case of chronic miliary tuberculosis, a striking and apparently definitive result was obtained It was the problem of a subject already treated intensively with streptomycin and isoniazid, but without final success Cycloserine therapy resulted in total reabsorption of the miliary foci and recovery of the concomitant laryngitis In the other case, the result was poor

In the empyema case treated, we did not observe any favorable result More particular clinical details will be given in a few months when therapy in the remaining cases will be completed At this time, we feel we will be able to support our observations by the results of one year of clinical study

C) *From the bacteriologic point of view,* it is possible to state that following the first month of therapy, about one half of the patients became negative on direct examination This finding remained constant and at the end of the eighth month of therapy, of the 26 patients positive for tubercle bacilli initially, 13 became negative on direct examination,

and of the 27 positive for tubercle bacilli on culturing, eleven have become negative (40 per cent)

D) *Collateral negative phenomena* were nearly of a slight degree and of five types·

1 In two cases, an *urticaria* was noted after about 20 days of therapy, with complete disappearance on discontinuing therapy

2. In eleven cases, during the first 15-20 days of treatment, a minimal arterial hypotension was noted This disappeared spontaneously with no interruption of therapy

3 In twelve cases, drowsiness, followed by cephalgia, adinamia, and psychia depression had appeared with the first 48 hours These symptoms disappeared after one-two weeks, cycloserine administration continuing uninterrupted

4 In nine patients, a sudden rise of the fever was noted within the first 48 hours and this persisted for two to four days This secondary rise probably occurred secondary to the reabsorption of tuberculin products coming from the bacillary bodies or from the products of tissue degeneration within the lesions This mechanism is thought to be similar to the phenomenon of the immunological crisis described by E Morelli and G Daddi at the very beginning of therapy with isoniazid

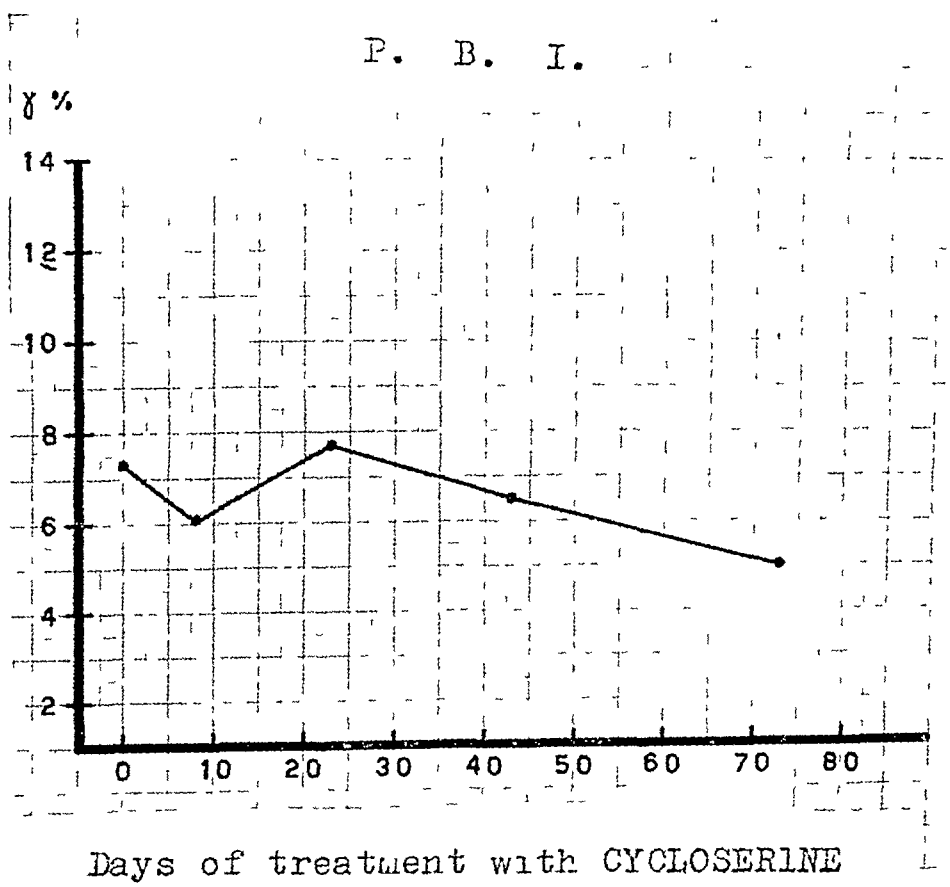


FIGURE 7

5 In three cases, severe side effects related to involvement of the nervous system were observed, manifested by periods of strong psychomotor agitation, alternating with periods of drowsiness and followed by schizoid phenomena in one case One patient attempted suicide In two cases, it has been possible to continue therapy following an interrupted period of one to two weeks and a good clinical result was obtained In the third case, the therapy was completely stopped Involvement of the C N S is less frequent, when the dosage is carefully regulated and a more selective choice of patients is effected

In addition to the above mentioned phenomena, symptoms were noted in two patients at about the 45th day of therapy and a questionable relationship to cycloserine is postulated These symptoms were characterized by a sense of thoracic constriction, dyspnea at minimal effort, and without objective evidence of impaired cardiorespiratory function or bronchospasm These symptoms disappeared spontaneously after two to three days, the interruption of cycloserine therapy not being necessary

E) In four cases, noted reported in the above mentioned table, for which cycloserine was administered by endocavitary way (four women who had undergone a treatment of lobor etraction according to the technique of Omodei Zorini, Bottari and Di Paola) the drug was introduced in the dose of 0 50 gr divided into two daily doses and accompanied by endocavitary aspiration according to the method of Monaldi No general

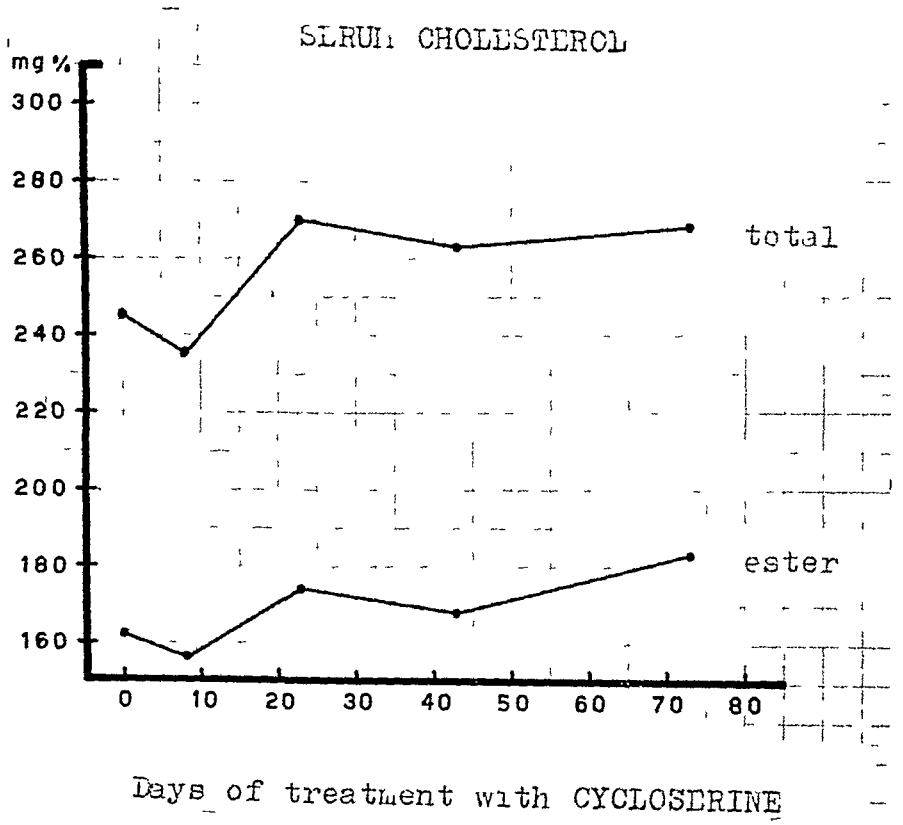


FIGURE 8

or local disturbances were noted and the endocavitary secretion became negative for tubercle bacilli after a therapeutic period of two to six weeks In three patients, the so-treated cavitations were nearly completely eliminated, and in two of them, an apico-axillary thoracoplasty procedure was done

In addition to routine clinical investigations, a number of biochemical, biologic, and hematologic examinations were carried out, the results of which we shall briefly report since this will be the first time some of the results will have appeared in the literature

1) *The precipitable bound iodine,* after an initial decrease, showed a sudden increase at the 23rd day, subsequently falling below the starting values (Figure 7)

2) *Cholesterol and cholesterol-esters* follow essentially the behaviour of P B I, remaining however slightly higher than the starting values by the end of the observation period (Figure 8)

3) *Serum proteins* showed marked variations the *total proteins* in-

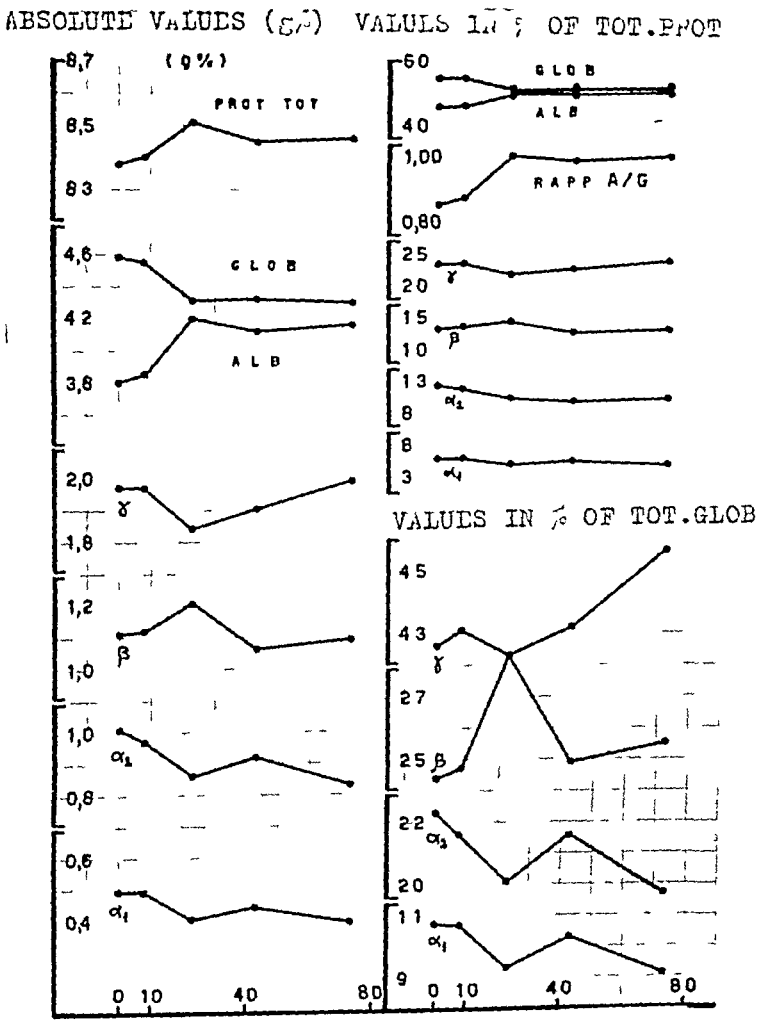


FIGURE 9

creased gradually until the 43rd day, at which time a slight decrease was noted, the serum levels remaining above the initial values, however, *total globulin* underwent a marked decrease until the 73rd day of therapy, in the meantime, *albumin* increased considerably until the end of the therapy, so that A/G ratio previously altered has returned to the initial values by the 23rd day and remains thus to the end of the observation period As for the *globulin fractions*, a tendency to decrease is observed for all of them, with only an initial decrease noted for gamma globulin

In evaluation of the respective globulin decrease in terms of percentage, it is readily deduced that the overall decrease is concerned especially with alpha 1 and with alpha 2 globulin (Figure 9), while gamma globulin clearly tends to increase with the time The *plasma fibrinogen* presents a steady decrease from the beginning to the end of the observation period, behaving in the opposite manner observed during pyrazinamide therapy (Figure 10)

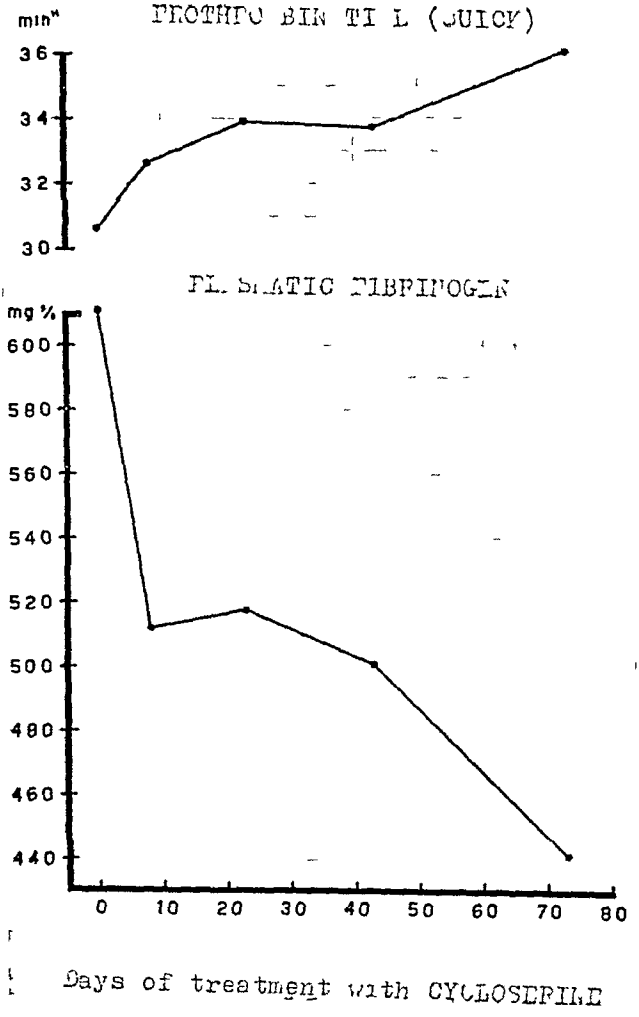


FIGURE 10

4) *The prothrombin time* from the beginning shows a prolongation which persists until the end of therapy (Figure 10)

5) *The Thorn index* showed a steady decrease over the entire observation period, of the number of circulating eosinophils of the uric acid/creatinin ratio, of azoturia Also, urinary 17-ketosteroid were noted to have a tendency to decrease

6) From the study of *the peripheral blood counts,* we have observed for both the white and the red series a slight increase of mean values

7) *The plasma lipasic power* has progressively *increased* (Figure 11)

8) *Specific proteases of defense in urine* showed an initial increase, followed by a decrease, this pattern of behavior being opposite to that observed during pyrazinamide therapy (Figure 11)

As for clinical and functional liver behavior (Mariani), it is possible to state that contrary to what happened during the pyrazinamide therapy cycloserine did not cause any toxic reactions to the liver, and furthermore, it behaved almost like a protective agent

There were some subjects in whom evidence of severe liver dysfunction was not noted at the start of therapy, but in whom minimal alteration of liver function was present In these cases, even these minimal signs of hepatic dysfunction diminished during the course of therapy In other cases, demonstrating even more severe clinical evidence of hepatic dysfunction, further resolution was noted during therapy

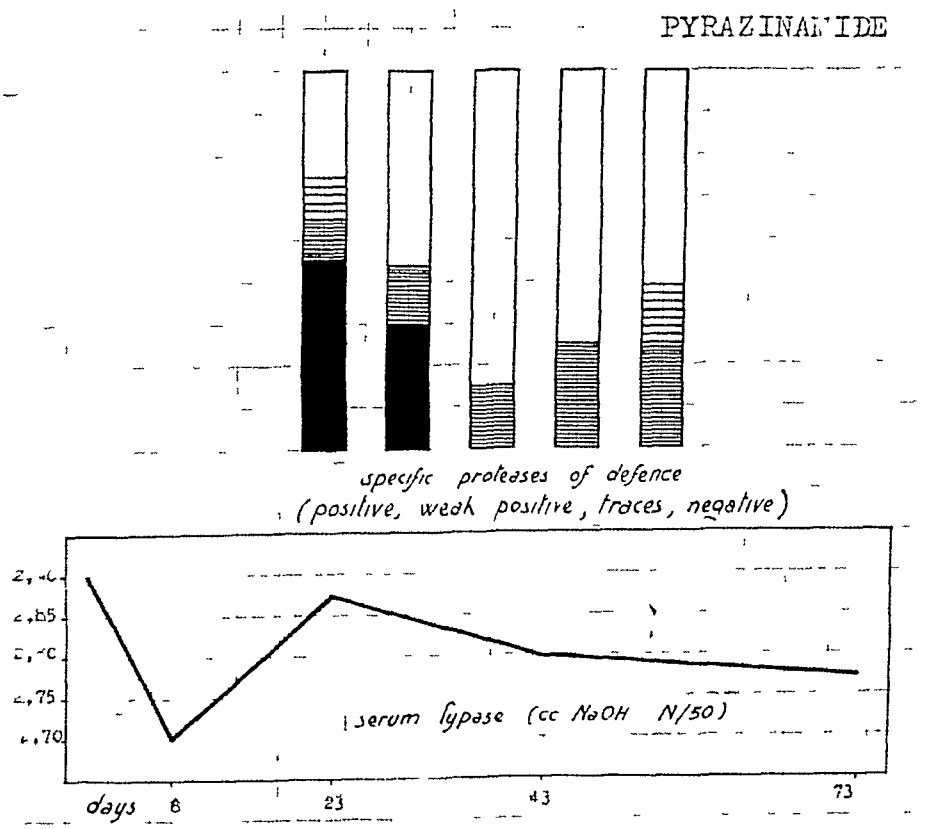


FIGURE 11

The graph based on mean values of the casuistry, clearly shows this behavior before, during, and at the end of therapy

Clinical, subjective, and objective liver findings were in agreement with data given by the laboratory tests

In conclusion, we can state that cycloserine has induced in two thirds of the treated patients an appreciable clinical improvement and significant modifications of the roentgenographic picture featured by cavity closure and regression of exudative and miliary foci in 36 per cent of patients In about 40 per cent of subjects initially positive for tubercle bacilli, the sputum became negative on both direct smear and culture Although we recognize that the number of cases included in this study is too small to make unequivocal deductions, nevertheless, after eight months of clinical observation, supported by a number of laboratory tests, it is possible to state that cycloserine is a new drug with definite therapeutic activity against human tuberculosis, showing marked therapeutic effects in recent forms, and a lesser degree of efficacy in a certain number of chronic cases which have become resistant to the well-known and widely used drugs

SUMMARY

1 A series of clinical and biological investigations on pyrazinamide and cycloserine in the treatment of pulmonary tuberculosis are reported

These investigations were accompanied by the following laboratory studies serum electrophoresis, phagocytic index, precipitable bound iodine, adrenal cortical function, behavior of specific proteases of defense in urine, plasma lipasic power, serum cholesterol, serum bilirubin, plasma fibrinogen, prothrombin time, and finally with the serolability tests and the charge tests of liver function

Pyrazinamide showed a favorable action on tuberculous lesions in a limited number of cases and for a short duration, not exceeding 35-40 days of therapy, following which toxic phenomena were observed, predominantly hepatic The laboratory tests in this subsequent period of study showed increasing variance from normal values, with an increase of the precipitable bound iodine and a dissociation between the globulin with an increase in the beta and a decrease in the gamma fraction

2 Cycloserine, on the basis of our studies, was thought to be a more patient antibiotic, manifested by definite improvement in the x-rays of both fresh exudative cases, as well as in cases of chronic cavitary disease, some of these being resistant to the usual therapeutic measures, with appreciable regression of the far advanced cavitations, and conversion of a positive sputum to negative in both types of cases Its toxic action on the central nervous system is not frequent and does not usually interfere with the continuance of therapy The laboratory tests have generally shown normal values even after the second and third month of therapy with the precipitable protein bound iodine, serum proteins, and particularly beta gamma globulin, plasma fibrinogen, prothrombin time, plasma lipasic power, specific proteases of defense in urine, and the charge tests for liver function, presenting a behavior opposite to that of pyrazinamide

RESUMEN

1 Se relatan una serie de investigaciones clínicas y biológicas sobre pirazinamida y cicloserina en el tratamiento de la tuberculosis pulmonar

Estas investigaciones se acompañaron de los siguientes estudios de laboratorio electroforesis del suero, índice fagocitario, yodo compuesto precipitable, función córtico suprarrenal, suerte de las proteasas específicas de defensa en la orina, poder lipásico del plasma, colesterol sanguíneo, bilirrubina en el suero, fibrinógeno del plasma, tiempo de proptrombina, y finalmente, pruebas de serolabilidad y las pruebas de carga de la función hepática

La pirazinamida mostró una acción favorable sobre las lesiones tuberculosas en un numero limitado de casos y por corto tiempo que no sobrepasó de 35-50 días de tratamiento siguiendo fenómenos tóxicos con predominio de los hepáticos Las pruebas de laboratorio en este subsecuente período de estudio, mostraron variación creciente desde los valores normales con un aumento del yodo ligado precipitable y una disociación entre la globulina con un aumento de la beta y disminución de la fracción gama

2 La cicloserina, basandonos en nuestros estudios, se encontró más potente como antibiótico según el cambio manifiesto a los rayos X tanto en los casos de lesiones exudativas recientes, como en los casos de cavitarios crónicos, algunos de estos aún siendo resistentes a los recursos terapéuticos habituales con una regresión apreciable de las excavaciones en los muy avanzados y conversión de positivos a negativos en esputos en ambos tipos de enfermedad Su acción tóxica sobre el sistema nervioso central no es frecuente y generalmente no interfiere con la continuación del tratamiento Las pruebas de laboratorio generalmente han mostrado valores normales aún después del segundo y tercer mes de tratamiento con todas las pruebas mencionadas al principio de este resumen comportándose de manera opuesta a la pirazinamida

RESUME

Les auteurs rapportent une série d'investigations cliniques et biologiques sur le traitement de la tuberculose pulmonaire par la pyrazinamide et la cyclosérine

Ces investigations étaient accompagnées des études de laboratoire suivantes électrophorèse du sérum, index phagocytique, étude de la précipitation iodée, fonction adréno-corticale, comportement des protéases spécifiques de défense dans les urines, pouvoir lipasique du plasma, dosage du cholestérol, de bilirubine, du fibrogène plasmatique, temps d'action de la prothrombine, et enfin tests d'instabilité du sérum, et tests de charge de la fonction hépatique

La pyrazinamide montra une action favorable sur les lésions tuberculeuses dans un nombre limité de cas, et pendant un temps court n'excédant pas 35 à 50 jours de traitement, après cela des phénomènes toxiques, principalement hépatiques, furent observés Les tests de laboratoire dans cette phase postérieure de l'étude montrèrent des taux en augmentation par rapport aux valeurs normales, avec un accroissement du pouvoir précipi-

tant de l'iode et une dissociation des globulines avec une augmentation de la beta globuline et une diminution de la fraction gamma

2 D'après ces etudes, la cyclosérine peut être tenue pour un antibiotique plus efficace, ceci étant démontré par l'amélioration radiologique incontestable, aussi bien des cas exsudatifs récents que des cas d'affections cavitaire chronique, quelques-une de ces cas étaient résistants aux moyes thérapeutiques habituels et il y eut une régression appréciable des processus cavitaires très avancés, et la négativation bactériologique des expectorations dans les deux exemples de ces cas Son action toxique sur le système nerveux central n'est pas fréquente, et ne trouble généralement pas la poursuite du traitement Les tests de laboratoire ont montré des valeurs généralement normales, même après le deuxième et le troisieme mois de traitement selon le test de précipitation iodée, le test des protéines sériques, et surtout le test à la globuline beta et gamma, le fibrinogène plasmatique, le temps de prothrombine, le pouvoir lipasique du plasma, les protéases spécifiques de défense dans les urines, et les tests de charge de la fonction hépatique, qui présentèrent un comportement opposé à celui des tests obtenus au cours du traitement par la pyrazinamide

ZUSAMMENFASSUNG

1 Bericht uber eine Reihe von klinischen und biologischen Untersuchungen uber Pyrazinamid und Cycloserin bei der Behandlung der Lungentuberkulose

Diese Untersuchungen erfolgten in Verbindung mit folgenden Laboratoriumsuntersuchungen Serum-Elektrophorese, Phagocyten-Index, ausfallbares gebundenes Jod, Nebennierenrinden-Funktion, Verhalten von spezifischen Abwehrproteasen im Urin, Plasma-Lipase-Vermogen, Serum-Cholesterin, Serum-Bilirubin, Plasma-Fibrinogen, Prothrombin-Zeit und schliesslich Serum-Labilitats-Prufungen und die Belastungsteste der Leberfunktion

Pyrazinamid zeigte einen gunstigen Einfluss auf tuberkulose Herde in einer begrenzten Zahl von Fallen und fur eine kurze Dauer, die keine 35-50 Behandlungstage uberschritt und im Anschluss daran toxische Phanomene zeitigte, vorwiegend von Seiten der Leber Die Laboratoriumsuntersuchungen wahrend dieser anschliessunden Prufungsperiode zeigten eine zunehmende Abweichung von normalen Werten mit Anstieg des ausfallbaren gebundenen Jods und einer Dissociation innerhalb der Globuline mit einem Anstieg in der Beta- und einer Abnahme in der Gamma-Fraktion

2 Von Cycloserin wurde auf Grund unserer Untersuchungen angenommen, dass es ein vorzuglicheres Antibioticum sei, wie dies zum Ausdruck kommt durch definitive Besserung in den Rontgenbildern sowohl von frischen exsudativen Fallen, als auch von Fallen mit chronisch-cavernoser Krankheitsform, von denen einige resistent waren gegenuber den gewohnlichen therapeutischen Massnahmen mit merklicher Ruckbildung der weit fortgeschrittenen Cavernisierungen und Erlangung von Bazillenfreiheit bei beiden Krankheitsformen Sein toxischer Einfluss auf das Zentralnervensystem ist nicht haufig und hindert fur gewohnlich nicht die Fort-

setzung der Therapie Die Laboratoriumsuntersuchungen zeigten im Allgemeinen normale Werte, sogar nach dem 2 und 3 Behandlungsmonat hinsichtlich des ausfallbaren am Eiweiss gebundenen Jods, der Serum-Proteine und besonders Beta- und Gammaglobulin, Plasma-Fibrinogen, Prothrombin-Zeit, Plasma-Lipase-Vermogen, spezifischer Abwehrproteasen im Urin und den Belastungsproben fur die Leberfunktion—ein Verhalten, das demjenigen bei Pyrazinamid sich als entgegengesetzt erweist

REFERENCES

1 Anderson, R C, Worth, H M, Welles, J S and Chen, K R "Pharmacology and Toxicology of Cycloserine," *Antibiotics and Chemotherapy*, 6 360, 1956

2 Daddi, G, Corda, M, Grassi, G and Basilisco, F "Prime osservazioni cliniche sul trattamento della tbc polmonare con pirazinamide," *Giornale Italiano della tuberculosi*, 10, 1956

3 Epstein, J G, Nair, G S and Boyd, L J "The Treatment of Human P Tbc with Cycloserine Progress Report," *Dis Chest*, 29 241, 1955

4 Phillips and Horton, G E "Pyrazinamide Isoniazid Comparison with Isoniazid Para-aminosalicylic Acid in Active P Tbc with the Choice of Regimens Determined by Chance," *Am Rev Tuberc*, 73 704, 1956

5 Omodei Zorini, A, Spina, G and De Simoni, G Comunicazione presso Associazione Laziale di Tisiologia (27 giugno 1956)

6 Omodei Zorini, A, Spina, G and De Simoni, G Comunicazione presso Accademia Medica di Roma (13 luglio 1956)

7 Rendig, J V, Sol Charen and Lepina, L T "Psychological Side Effects Induced by Cycloserine in the Treatment of P Tbc" *Am. Rev Tuberc*, 73 438, 1956

8 Renzetti, A D "Clinical, Bacteriologic, and Pharmacologic Observations upon Cycloserine," *Am Rev Tuberc*, 74 128, 1956

9 Steenken, W and Wolinsky, T "Cycloserine Antituberculous Activity in Vitro and in Tbc Experimental Animal," *Am. Rev Tuberc*, 73 539, 1956

10 Omodei Zorini, A, Spina, G, De Simoni, G Sulle possibilità di impiego terapeutico dei nuovi preparati ad azione antitubercolare (Pirazinamide e Cicloserina) Nota preventiva," *Minerva Medica*, 47 80, 1956

Circumscribed Intrapulmonary Hematoma Presenting as a "Coin" Lesion

HOWARD A BUECHNER, M D , F C C P * and JORDAN THOMPSON, M D *
New Orleans, Louisiana

In recent years the problem of solitary circumscribed pulmonary nodules has attracted much attention in the medical literature The difficulties involved in establishing an accurate diagnosis in cases of this kind are well recognized and are usually resolved by resort to exploratory thoracotomy and excision of the lesion That this approach to the problem is rational and well founded is amply substantiated by the many excellent reviews on the subject which have established an incidence of malignancy in such cases varying from approximately 7 to 74 per cent and averaging about 37 per cent [1-9] The major portion of this group is, of course, comprised by primary bronchogenic carcinoma, while metastatic tumors and other primary malignant diseases such as bronchial adenoma, sarcoma or lymphoblastoma make up a much smaller component Non-malignant lesions which most commonly present as isolated pulmonary nodules are tuberculomas, granulomas of nonspecific origin, hamartomas, histoplasmomas and coccidioidomas In addition to the above disorders there is a great variety of less common and even rare conditions which may assume the form of "coin" lesions and with which the physician must be familiar if he is even to consider the correct diagnosis prior to surgical exploration of the chest To but mention some of these diseases—chronic organized pneumonitis, lung abscess, bronchogenic cyst, pleural mesothelioma, lipoid granuloma, neurofibroma, pulmonary infarct, encapsulated pleural effusion or empyema, blastomycosis, cryptococcosis, hemangioma, hydatid cyst, fibrin body and brucellosis may all appear as solitary circumscribed pulmonary nodules

The following report purports to add to this list another condition which hitherto has received but little attention, that is, intrapulmonary hematoma

Persistent, circumscribed, intrapulmonary hematomas must be either extremely rare in occurrence or generally unrecognized if one can judge from the few cases which have appeared in the literature

Although a number of authors[10-13] have briefly described or referred to hematoma formation in the lung, the roentgenographic changes produced by these lesions have been variously indicated as "spindle shaped"[10, 13] or "ill defined"[11, 12] and have not presented the sharply circumscribed, round or oval appearance of the so called "coin" lesion Only the three cases reported by Salyer, Blake and Forsee[14] and the single

From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, The Tulane University of Louisiana School of Medicine
Chief, Medical Service, Veterans Administration Hospital
*Chief, Tuberculosis Section, Veterans Administration Hospital

case mentioned by Condon[15] fall into this category To this group a fifth such case is added in the following report

Case Report G C H, a 60 year old white male cook, was admitted to the hospital on May 5, 1954, for the treatment of an inguinal hernia A routine admission roentgenogram of the chest disclosed the presence of a sharply outlined circular density in the right lower lung field and this lesion then became the object of major diagnostic interest History disclosed that the patient had enjoyed relatively good health until December, 1949, when he developed the onset of sudden severe pain in the low back region He was admitted to the hospital at that time, where roentgenograms of the skeletal system disclosed generalized demineralization associated with collapse of the first lumbar vertebra together with anterior wedging of several thoracic vertebrae Roentgenographic examination of the chest disclosed a healing fracture of the anterior aspect of the right seventh rib but no evidence of a parenchymal lesion A diagnosis of multiple compression fractures of the vertebrae due to senile osteoporosis was established and he was discharged in January, 1950, after satisfactory response to rest and the application of a back brace In August, 1953, he fell and sustained a fracture of the right hip He was treated at another hospital and apparently made an uneventful recovery Thereafter he did well until February, 1954, when he developed a "cold" associated with nonproductive cough, fever and severe pain in the right posterior chest Treatment at a local outpatient clinic resulted in prompt improvement, although the thoracic pain persisted for three weeks An x-ray film of the chest on February 16, 1954, disclosed no abnormality other than "bilateral emphysema" In the latter part of March, 1954, he fell and struck the right side of his thorax Soreness at the site of injury gradually subsided in approximately two weeks During this period he complained of mild exertional dyspnea and noted an alleged decline in weight from 165 to 138 pounds, but he sought no further medical attention until the present admission when he entered the hospital for the aforementioned hernia repair

Physical Examination On admission to the hospital he appeared to be well developed and well nourished He was mentally alert and showed no evidence of acute illness Temperature 98 0°, pulse 84, blood pressure 160/110 The thorax appeared to be narrowed and exhibited an increased anterior posterior diameter Breath sounds were generally diminished in intensity and the percussion note was hyperresonant over both lung fields Other physical findings included evidence of generalized arteriosclerosis, prostatic hypertrophy, bilateral varicosities of the lower extremities, prominent kyphosis of the dorsal spine and a reducible, indirect, left inguinal hernia

Laboratory and X-ray Film Findings Roentgenograms of the chest disclosed a sharply circumscribed rounded lesion in the lower lobe of the right lung (Figures 1, 2, and 3) The shadow measured 3 5×4 0 cm in diameter and appeared to be homogenous but of low density Although the lesion apparently touched the pleura posteriorly it seemed to be entirely located within the lung parenchyma The remainder of the lung fields showed evidence of emphysematous changes Healing fractures of the right seventh posterior rib and the posterior portions of the left eighth and ninth ribs were noted A complete bone survey disclosed marked generalized demineralization throughout the skeletal system There had been some progression of the multiple vertebral compressions since previous films of December, 1949 An intravenous pyelogram, a gastrointestinal series and a barium enema were negative Tuberculin skin test (PPD) gave a positive reaction while testing with coccidioidin and histoplasmin was negative Sulkowitch's test disclosed no increase in urinary calcium Serum calcium 10 5 mg per cent, serum phosphorous 3 5 mg per cent, alkaline phosphatase 6 0 Bodansky units, acid phosphatase 07 K A units Sputum, blood count, urinalysis, liver function studies and stool examinations were negative

Course in Hospital When diagnostic studies failed to clarify the etiology of the pulmonary nodule, the right thorax was entered through the bed of the excised seventh rib on June 2, 1954 A "cystic" lesion,

FIGURE 1

FIGURE 2

FIGURE 3

Figure 1 Erect posterio-anterior roentgenogram of the chest showing a sharply outlined circular density in the right lower lung — *Figure 2* Right anterior oblique roentgenogram of the chest illustrating the posterior location of the lesion Although it touches the chest wall it appears to be completely located within the lung parenchyma —*Figure 3* Body section roentgenogram illustrating the discrete outlines and homogeneous character of the lesion

the size of a "golf ball" was encountered in the posterior aspect of the right lower lobe Approximately one third of the lesion protruded subpleurally, while the remainder was buried in the parenchyma of the lung The specimen, removed by "snip" resection, consisted of fluctuant mass which, when opened, was found to be cystic and contained approximately 6 cc of dark red blood with some irregular small clots When the blood was washed away the lining of the cyst was white and finely granular with some red fibrin strands attached The wall of the cyst was less than 1 mm in thickness, it appeared dense and fibrous Microscopic examination disclosed a well-organized cyst wall surrounded by compressed lung parenchyma externally Fragments of fibrin and degenerating blood were attached to the inner cyst wall (Figure 4) The pathological diagnosis was hemorrhagic cyst, post-traumatic (organized pulmonary hematoma) Microscopic study of the resected rib disclosed osteoporosis and a healing fracture

The postoperative course was uneventful On June 29, 1954, a left inguinal hernioplasty was carried out and on October 5, 1954, he underwent transurethral resection of the prostate On October 20, 1954, he was discharged from the hospital He was last seen when rehospitalized following a fall which caused severe pain in the lower back This com-

FIGURE 4 Photomicrograph of a section of the wall of the hematoma demonstrating its well organized fibrotic character Shreds of fibrin can be seen on the inner surface of the cyst while compressed lung tissue is visualized externally

plaint responded to rest and the application of a lumbosacral corset X ray films of the chest were unchanged and he was discharged on January 19, 1956

Discussion

Results of trauma to the lung or pleura are usually easily recognized A clear-cut history of injury, either penetrating or nonpenetrating, is almost always obtained and physical evidence of trauma is seen in the form of rib fractures or contusions of the chest wall If these findings are further associated with the typical roentgenographic appearance of hemothorax, pneumothorax or pneumohemothorax, it is easy to ascertain that injury to the pleura has occurred

Violence to the chest may also injure the pulmonary parenchyma without apparent evidence of pleural perforation Roentgenographic findings are less characteristic, in such cases, but usually reflect the results of hemorrhage and edema within the lung substance Areas of diffuse infiltration or consolidation are seen, sometimes associated with an atelectatic component resulting from intrabronchial bleeding The nature of these findings is further clarified by their tendency toward prompt regression during a period of a week or more

Where the intrapulmonary bleeding is localized and becomes sharply circumscribed into the form of a solitary hematoma the diagnosis becomes less certain, since this type of lesion may be clinically indistinguishable from a primary bronchogenic carcinoma or any other condition which can assume the appearance of a "coin" lesion In spite of a history of trauma, the presence of rib fractures or evidence of other injury to the chest, the physician is now confronted by an indeterminate pulmonary lesion, the exact nature of which can be established only by resort to exploratory thoracotomy This was the situation in the cases reported by Salyer et al[14] and in the patient we described

Since all of the sharply circumscribed intrapulmonary hematomas thus far reported have been surgically excised, little is known of their ultimate fate In describing poorly defined hematomas of the lung secondary to blast or nonpenetrating injury McGrigor and Samuel[12] state that resolution of the lesion may take as long as six to eight weeks Blain[11] indicates a similar course for hematomas of this type In 1950 Welkind[13] reported what was probably the first case of a sharply circumscribed pulmonary hematoma to appear in the medical literature The lesion was described as "a tumor-like shadow consisting of two spindle masses which fused at their axillary ends" Resolution gradually took place over a period of 13 months, leaving two persistent linear scars The author felt it to be "inconceivable that a simple hematoma would take 13 months completely to resorb," and postulated that the lesion was associated with an element of infarction or that it was possible "some sort of thick capsule formed around the clotted blood, retarding the resolution" He closed his paper with the prediction that final solution of the problem would come only from postmortem studies of hematomas months or years after injury In 1953 Salyer et al[14]

provided such a solution when they removed three localized pulmonary hematomas by surgical resection Two of these lesions were described as cystic cavities filled with clotted blood Similar pathological changes were, of course, encountered in our own case As Welkind[13] postulated, it is undoubtedly the cyst formation which accounts for the persistent nature of these lesions Just how long a well organized encapsulated hematoma might remain unchanged within the lung is still a matter for speculation Although our patient was observed for only one month prior to resection, in two of Salyer's[14] cases the lesions exhibited no tendency toward resolution over periods of eight and 12 weeks In Salyer's[11] third patient the hematoma showed no change in size during a period of three and a half months, but a bronchial communication developed and the cyst underwent partial evacuation of its contents, leading the authors to speculate on the dangers of chronic suppuration or flank abscess formation This complication indicates that at least some of these lesions may be regarded as potentially dangerous to the patient However, it seems likely that in most instances the hematoma would exhibit gradual resolution, as in Welkind's[13] case, while in others it would persist for even longer periods, eventually undergoing fibrosis or perhaps calcification

SUMMARY

1 A case of solitary, sharply circumscribed, intrapulmonary hematoma following non-penetrating injury of the chest is reported The hematoma presented as a "coin" lesion clinically indistinguishable from a peripheral bronchogenic carcinoma or other conditions known to produce discrete pulmonary nodules

2 The shape, the sharp outline and the tendency of these lesions to persist unchanged within the lung for long periods can apparently be ascribed to the formation of a fibrotic cyst wall around the hematoma

3 Pulmonary hematomas of this type appear to be distinctly rare, but should be considered in the differential diagnosis of isolated discrete nodules of the lung, particularly if there is a prior history of chest trauma or evidence of rib fracture Even though the nature of such a lesion is suspected, exploratory thoracotomy will usually be required in order to establish the correct diagnosis

RESUMEN

1 Se relata un caso de un hematoma después de una herida no penetrante de tórax, el que fué solitario, y bien circunscrito Esehematoma revistió el aspecto de una lesión de las llamadas en "moneda," clínicamente indistinguible de un carcinoma bronquiogénico periférico o de otras afecciones que se sabe producen nódulos discretos en el pulmón

2 La forma, el contorno limitado y la tendencia de estas lesiones a persistir sin cambios dentro del pulmón por largo tiempo, puede atribuirse a la formación de una pared de quiste fibroso alrededor

3 Estos hematomas son raros pero deben tenerse presentes en el diag-

nóstico diferencial de los nódulos asilados y discretos del pulmón especialmente si hay antecedente de trauma del tórax o fractura de costilla

Aunque la naturaleza de estos se sospeche la toracotomía exploradora se requerirá para aclarar el diagnóstico

RESUME

1 Les auteurs rapportent un cas d'hématome intrapulmonaire isolé, très circonscrit, faisant suite à un traumatisme non pénétrant de la poitrine L'hématome se présentait comme une lésion en "pièce de monnaie," qui ne pouvait pas se différencier d'un cancer bronchique péhiphérique ou d'autres états connus pour produire des nodules pulmonaires discrets

2 La forme, le tracé précis, la tendance de ces lésions à persister sans changement a l'intérieur du poumon pendant de longues périodes, peuvent apparemment être attribuées à la formation d'une paroi fibro-kystique autour de l'hématome

3 Les hématomes pulmonaires de ce type semblent être rares, mais devraient être pris en considération dans le diagnostic différentiel des nodules discrets isolés du poumon, particulièrement s'il y a auparavant une histoire de traumatisme thoracique ou la preuve d'une fracture de côte Même quand on suspecte la nature d'une telle lésion, il sera généralement indiqué de pratiquer une thoracotomie exploratrice pour affirmer le véritable diagnostic

ZUSAMMENFASSUNG

1 Bericht uber einen Fall eines solitaren, scharf umschriebenen intrapulmonalen Hamatoms im Anschluss an ein stumpfes Trauma des Brustkorbes Das Hamatom stellt einen "Rand"—Herd dar und ist klinisch nicht zu unterscheiden von einem peripheren, bronchogenen Carcinom oder anderen Affektionen, von denen bekannt ist, dass sie zur Bildung von diskreten pulmonalen Knotchen fuhren

2 Die Gestalt, die scharfe Begrenzung und die Tendenz dieser Herde, unverandert in der Lunge fur lange Zeitraume bestehen zu bleiben, kann augenscheinlich die Bildung einer fibrotischen Cystenwand um das Hamatom herum zugeschrieben werden

3 Pulmonale Hamatome dieses Types scheinen ausgesprochen selten zu sein, man muss sie jedoch in Erwagung ziehen bei der Differential-Diagnose isolierter diskreter Knotenbildungen der Lungen, besonders wenn in der Vorgeschichte ein Thorax-Trauma vorkommt, oder der Befund einer Rippenfraktur besteht Aber selbst wenn man die Natur einer solchen Veranderung vermutet, wird eine diagnostische Thorakotomie fur gewohnlich notwendig sein, um eine genaue Diagnose sicher zu stellen

REFERENCES

1 Mahon, H W and Forsee, J H "The Surgical Treatment of Round Tuberculous Pulmonary Lesions (Tuberculomas," *J Thoracic Surg*, 19 724, 1950

2 Thornton, T F, Jr, Adams, W E and Bloch, R G "Solitary Circumscribed Tumors of the Lung," *Surg, Gynec and Obst*, 78 364, 1944

3 Effler, D B, Blades, B and Marks, E "Problem of Solitary Lung Tumors," *Surgery*, 24 917, 1948

4 Bugden, W F "Asymptomatic and Circumscribed Lesions of Chest," *Am Rev Tubere*, 62 512, 1950

5 Hood, R T, Jr, Good, C A, Clagget, O T and McDonald, J R "Solitary Circumscribed Lesions of Lung Study of 156 Cases in which Resection was Performed," *J A M A*, 152 1185, 1953

6 Storey, C F, Grant, R A and Rothmann, B F "Coin Lesions of Lung," *Surg, Gynec and Obst*, 97 95, 1953

7 Davis, E W, Katz, S and Peabody, J W, Jr "Surgical Implication of Solitary Tumors of the Lung," *Am J Surg*, 89 402, 1955

8 Wilkins, E W, Jr "The Asymptomatic Isolated Pulmonary Nodule," *New England J Med*, 252 515, 1955

9 Ford, W B, Kent, E M, Neville, J F, Jr and Fisher, D L "'Coin' Lesions of the Lung," *Am Rev Tubere and Pulm Dis*, 73 134, 1956

10 Savage, O "Pulmonary Concussion ('Blast') in Non-Thoracic Battle Wounds," *Lancet*, 1 424, 1945

11 Blain, L G "Chest Manifestations in Abdomino-Thoracic Injuries," *Brit J Radiol*, 18 258, 1945

12 McGregor, D B and Samuel, E "The Radiology of War Injuries, Part III, War Wounds of the Chest," *Brit J Radiol*, 18 133, 1945

13 Welkind, A "Intrapulmonary Hematoma Due to Non-Penetrating Injury—Report of a Case," *Med Soc N J Journal*, 47 501, 1950

14 Salyer, J M, Blake, H A and Forsee, J H "Pulmonary Hematoma," *J Thoracic Surg*, 25 336, 1953

15 Condon, W B "Round Lesions of the Lung in Older Persons," *Thoracic Surg*, Seminar, Denver, Col, Fitzsimmons Army Hosp p 23, 1952

Pulmonary Tuberculosis and Peptic Ulcer*

ERNESTO WAINGORTIN, M D ** and HEINZ J LORGE, M D, F C C P †
Worcester, Massachusetts

For several years we have been impressed by the increasing frequency of gastric symptoms in patients with pulmonary tuberculosis The coexistence of this disease with peptic ulcer has been called to attention in Europe and in recent reports from the United States Our observations are illustrated by the analysis of 27 cases of pulmonary tuberculosis at Worcester County Sanatorium in which peptic ulcer was demonstrated either before admission or during the course of hospitalization Radiological proof of the ulcer is available in all cases Ulcers associated with neoplasm were excluded from this series The cases are divided into four categories

In the interpretation of these figures we should remember that not until recently did we become fully alert to the problem and to the need for a more detailed investigation of the gastrointestinal system in tuberculous patients In recent years we also had the opportunity to witness among our admissions the prevalence of tuberculosis in elderly men, a fact which was emphasized by the transfer of such patients from another hospital Only three of the cases were women The age of our patients at the time of admission ranged from 38 to 79 with an average of 55 The average age at the time of diagnosis was 50 for pulmonary tuberculosis and 48 for peptic ulcer In one the tuberculosis was moderately advanced All others had far advanced disease

The first group includes 12 patients who developed tuberculosis after surgery for peptic ulcer Nine had gastrectomy, total or subtotal, and two gastroenterostomy The last one had "closure" of a gastric ulcer but required gastrojejunostomy at a later admission The interval between abdominal surgery and onset of tuberculosis ranges widely from less than one year to 37 years In case seven the sequence of events is difficult to determine since the patient's lung disease may well antedate his operations

The second group is made up of four patients whose gastrointestinal symptoms appeared after surgical treatment of pulmonary tuberculosis by thoracoplasty The interval between operation and discovery of the peptic ulcer varies from four months to seven years In this group there were three duodenal and one gastric ulcers These patients also received chemotherapy including oral PAS medication before the onset of abdominal symptoms In case 13 a gastric ulcer developed in the wake of cortisone therapy for severe rheumatoid arthritis which complicated the tuberculosis

The third group includes seven cases in which pulmonary tuberculosis preceded the onset of peptic ulcer The latter was discovered at autopsy

*From the Worcester County Sanatorium
**Senior Physician, Worcester County Sanatorium
†Superintendent, Worcester County Sanatorium

in three, with signs of recent hemorrhage in two Six had received oral chemotherapy before the ulcer manifested itself Case 21 had extensive thoracic surgery within six weeks before his death, and a peptic ulcer was found at autopsy In three cases the ulcer was located in the stomach and in the other four in the duodenum

In the four cases of the fourth group, as in the first, the ulcers, one gastric and three duodenal, preceded the onset of tuberculosis but the treatment was medical rather than surgical

Discussion

In the past 10 years it has been commonly noted that an increasing number of patients admitted to tuberculosis hospitals showed the scar of previous gastrectomy This observation coincides with a strikingly large *proportion of patients who complain of "stomach upsets" or "heart burn"* and are found to be victims of peptic ulcer The literature now offers rather frequent reports which can generally be divided into two categories

a Pulmonary tuberculosis after gastrectomy for peptic ulcer

French writers were the first to discuss this relationship Isorni and associates[1] present 26 patients with gastrectomies among 742 admissions for pulmonary tuberculosis Thirteen of these had no manifestation of tuberculosis before operation The average interval between operation and the onset of pulmonary tuberculosis was three years In the United States, Warthin[2] finds that 2 per cent of 356 gastrectomized patients developed active pulmonary tuberculosis Allison[3] reports 21 cases of pulmonary tuberculosis following gastrectomy for peptic ulcer among

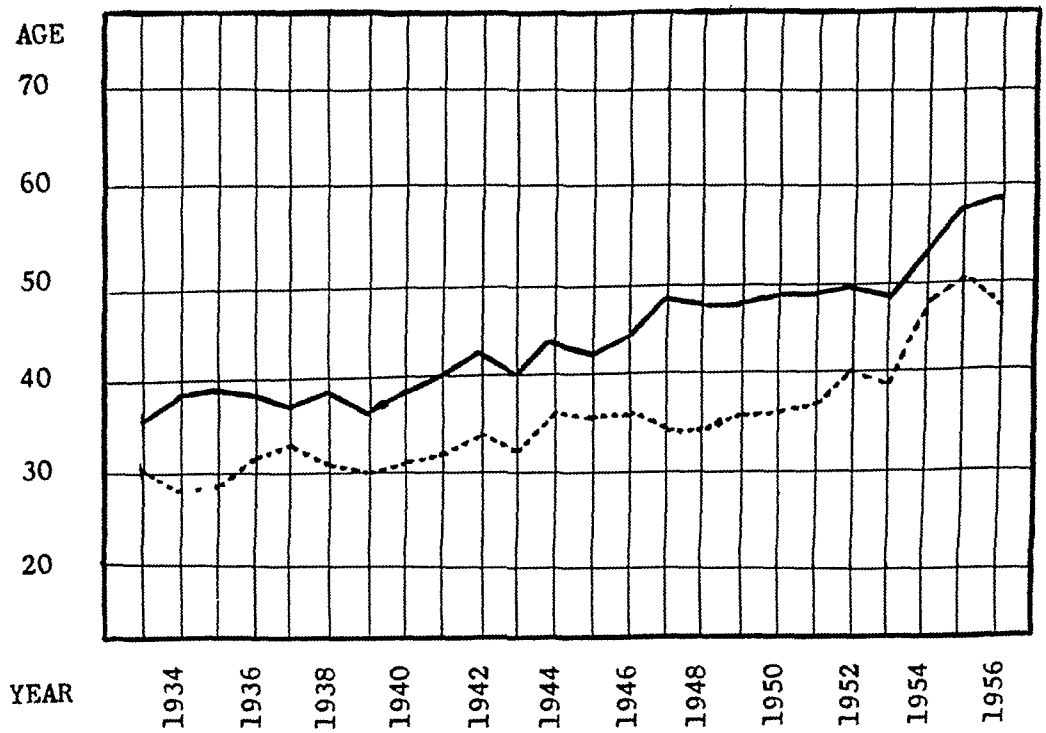


FIGURE 1 Average age of house patients at Worcester County Sanatorium, 1933 to 1956 *The solid line represents men, the broken line women*

admissions for five years with an average of 700 admissions per year The age of these patients ranged from 32 to 66 Seventeen had no previous evidence of tuberculosis, and in the other four the disease was considered inactive The infection was usually of the acute pneumonic type and resulted in a mortality of 25 per cent Boman[4] recently reported on 906 patients in four Swedish sanatoria Forty-three had a history of peptic ulcer which preceded the onset of tuberculosis in 32 and followed the onset of tuberculosis in 11 In 20 cases tuberculosis occurred following gastrectomy, and in three it was found prior to operation The author concludes that gastrectomy is a more important factor in the predisposition to tuberculosis than ulcers alone

b Peptic ulcer after treatment for pulmonary tuberculosis

In this group we only point to a recent report of Callanan[5] who studied 27 cases of peptic ulcer among admissions for pulmonary tuberculosis at London Chest Hospital for a period of five years Of the 23 who were subjected to some type of pulmonary surgery, 15 developed complications referable to ulcers, namely bleeding in eight and acute exacerbation of symptoms in seven Webber and Gregg[6] observed 70 patients with benign gastric ulcer of whom 43 per cent were found to have chronic pulmonary disease, an incidence which was 3 times as high as in randomized patients

The morbidity of peptic ulcers in this country has been estimated to range between 5 and 12 per cent The mortality rate in 1953 was 5 6 per 100,000 population[7] The death rate in men was six times as high as in women for gastric ulcer and seven times higher in duodenal ulcer Advances in medicine and surgery have bettered the longevity of the victims of peptic ulcer as well as those of pulmonary tuberculosis There has also been a steady increment in the incidence of tuberculosis in men of the older age group In England, the incidence in men over 65 years of age has risen from 50 to over 80 per 100,000 population since 1938[8] The average age of men at Worcester County Sanatorium has increased during the past 14 years from 40 to 58 (Fig 1), a period of life which coincides with that of the highest incidence of peptic ulcer One should also remember that peptic ulcer as well as pulmonary tuberculosis has been treated by surgical resection with mounting frequency

It has been suggested that chronic pulmonary disease, and particularly emphysema, produces electrolyte changes which in turn may result in increased secretion of acid and pepsin in the stomach, but Polster[9] has demonstrated that this sequence of events occurs only in mild cases of tuberculosis while in advanced disease the gastric acidity decreases Lucien[10] investigated the gastric chemistry of patients who had a history of dyspepsia or complained of it at the time of hospitalization None of 250 patients showed normal values One hundred sixty-three had elevated free and combined hydrochloric acid Forty-eight had elevation of free hydrochloric acid and only 39 had hypochlorhydria Lowell and associates[11] have emphasized the coincidence of smoking, emphysema and peptic ulcer

The important factor of physical and emotional stress in the pathogenesis of peptic ulcer has been reiterated in the past several years and is the subject of an excellent discussion by Gray [12] In this connection we are reminded that all 11 patients of our series who developed peptic ulcer following thoracic surgery or medical therapy had advanced pulmonary disease The presence of physical and emotional strain was conspicuous in almost every case

The theory which involves the irritating action of oral medication as a contributing factor in the development of peptic ulcer is well known The effect of acetylsalicylic acid upon the gastric mucosa is a fitting example Of the antituberculosis drugs para-amino-salicylic acid is most frequently responsible for gastrointestinal irritation in patients on oral chemotherapy and may justifiably be regarded as a contributing factor in the relapse of symptoms in chronic peptic ulcer Perhaps of equal importance in the discovery of peptic ulcers is the search for the actual cause of symptoms which have been erroneously interpreted as the result of drug intolerance

Another aspect of the problem is advanced by investigators who assume that electrolyte disturbances in the gastrectomized patient produce immunological changes resulting in the breakdown of the natural resistance of the lung parenchyma to the action of the tubercle bacillus We rather favor the theory that the profound inadequacy of nutrition which usually complicates the status of the gastrectomized patient explains in itself a disposition to pulmonary tuberculosis and recurrences in individuals with a history of previous disease

SUMMARY AND CONCLUSIONS

1 The coincidental occurrence of pulmonary tuberculosis and peptic ulcer has recently been observed with increasing frequency Twenty-seven cases are here reported

2 Tuberculous patients who develop gastrointestinal symptoms following thoracic surgery, oral chemotherapy, and especially PAS medication, should be investigated for peptic ulcer

3 Patients who are subjected to gastrectomy for peptic ulcer should have preoperative chest x-ray films If a pulmonary lesion is found, the presence of active tuberculosis should be ruled out After the operation the lesion should be carefully followed in the immediate postoperative period as well as in the distant future

4 Finally, a chest x-ray film should be part of the check-up examinations of all gastrectomized patients

RESUMEN Y CONCLUSIONES

1 La coincidencia de tuberculosis pulmonar y úlcera péptica se ha observado con creciente frecuencia Se han relatado 27 casos

2 Deben investigarse en busca de úlcera péptica los enfermos que han sufrido cirugía torácica, o han tenido quimioterapia oral en especial con PAS

3 Los sujetos a quienes se hace gastrectomía por úlcera péptica deben hacerse radiografía de tórax Si se encuentra una lesión pulmonar debe investigarse si se trata de tuberculosis Después de la operación la lesion debe ser cuidadosamente observada en postoperatorio inmediato y en el futuro distante

4 Finalmente, una radiografía de tórax debe formar parte de rutina de revisión de todos los gastrectomizados

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

1 Das gleichzeitige Vorkommen von Lungentuberkulose und Peptischem Geschwur ist in letzter Zeit mit zunehmender Haufigkeit beobachtet worden Hier wird über 27 Falle berichtet

2 Tuberkulose Patienten, bei denen sich im Anschluss an thoraxchirurgische Eingriffe gastrointestinale Symptome entwickeln oder nach oraler Chemotherapie und besonders PAS-Anwendung, sollten auf peptische Geschwure untersucht werden

3 Patienten, die wegen peptischem Geschwur einer Gastrektomie unterzogen werden, mussen vor der Operation eine Thorax-Rontgenaufnahme bekommen Wird ein Lungenbefund erhoben, muss das Bestehen einer aktiven Tuberkulose ausgeschlossen werden Nach der Operation muss der Befund sorgfaltig überwacht werden, sowohl während der unmittelbaren postoperativen Periode als auch in fernerer Zukunft

4 Schliesslich muss eine Thorax-Rontgenaufnahme zu einem Bestandteil der eingehenden Untersuchung aller gastrektomierten Patienten werden

REFERENCES

1 Isorny, Mlle Fabre, Le Monet, Baussan and Langeard "Gastrectomy and Tuberculosis," *Revue de la Tuberc*, 12 393, 1948

2 Warthin, T A "Reactivation of Pulmonary Tuberculosis in Relation to Subtotal Gastrectomy," *Am J M Sc*, 225 421, 1953

3 Allison, S T "Pulmonary Tuberculosis after Subtotal Gastrectomy," *New England J Med*, 252 862, 1955

4 Boman, K "Tuberculosis Occurring After Gastrectomy," *Acta Chir Scandinav*, 110 451, 1956 (*Abstracts Am Rev Tuberc and Pul Dis*, 74 134, 1956)

5 Callanan, J C "Gastrointestinal Complications Following Surgical Treatment of Pulmonary Tuberculosis A Report of Fifteen Cases," *Am Rev Tuberc and Pul Dis*, 74 358, 1956

6 Weber, J M and Gregg, L A "Coincidence of Gastric Ulcer and Chronic Pulmonary Disease," *Ann Int Med*, 42 1026, 1955

7 Metropolitan Life Insurance Co Statistical Bulletin, p 8-10, June, 1954

8 Wilkins, E G "Tuberculosis in Old Men," *Brit Med. Jour*, 4972 883, 1956

9 Polster, W "Studies on the Influence of Active Pulmonary Tuberculosis on Gastric Acidity," *Beitr Z Klin Tuberk*, 114 457, 1955 (*Abstracts Am Rev Tuberc, and Pul Dis*, 73 164, 1956)

10 Lucien, P "Gastric Chemistry in Dyspeptic Tuberculous Patients," *Rev de la Tuberc*, 12 368, 1948

11 Lowell, F C, Franklin, W, Michelson, A L and Schiller, I W "A Note on the Association of Emphysema, Peptic Ulcer and Smoking," *New England J Med*, 245 123, 1956

12 Gray, S *Principles of Internal Medicine*, edited by T R Harrison Second Edition New York The Blakiston Company, Inc, pp 1547-1563

13 Thorn, P A, Brooks, V S and Waterhouse, J A H "Peptic Ulcer, Partial Gastrectomy and Pulmonary Tuberculosis," *Brit Med Jour*, 4967 603, 1956

The Symptom of Sighing: Physiologic and Pathologic Observations*

GEORGE C LEINER, M D** and SOL ABRAMOWITZ, B A †
East Orange, New Jersey

A sigh is defined as a deep and prolonged audible inspiration and respiration of air, especially when involuntary and expressing some emotion or feeling as grief, yearning, weariness or relief [1]

Sighing is one of the characteristic patterns of most mammals, just as is eupnea, gasping and panting [2] It is common in humans Frequent sighing has for many years been considered a sign of nervous disturbance of respiration [3] and of neurocirculatory asthenia [4] Sighing is apparently due to a spasm of the diaphragm [5]

In the course of respiratory function studies in patients with various diseases of the lungs, heart and central nervous system sighing was observed not infrequently These observations appeared to be of interest and will, therefore, be presented in this paper

Material And Observations

In our observations we define a sigh as an involuntary respiratory peak that is 1 5 times or more the height of the tidal volume, this is slightly different from Caughey's definition,[6] according to which a sigh is twice as deep as the person's average breath

I Physiology of the Sigh

Four hundred and seventeen graphic records of the respiration (spirograms) of 330 individuals of the Medical and Tuberculosis Services of the Veterans Administration Hospital, East Orange, N J , were examined for the presence of sighs The spirograms were obtained by the routine method of determining the oxygen intake for basal metabolism studies and other pulmonary function data The Collins nine liter respirometer with ventilograph pen was used for all measurements Two six minute periods of quiet breathing of oxygen were examined for the presence of sighs All volumes were corrected to B T P S (body temperature, ambient pressure, saturated with water vapor)

Of the 330 individuals, four were normals, about two thirds had various forms of pulmonary tuberculosis and the remainder had various cardiac and pulmonary diseases

Of the 417 records, 93 were found to contain sighs Of the 330 individuals, 81 (24 5 per cent) were represented in the group of records having sighs Of the 81 individuals who sighed during quiet breathing 24 had repeat examinations Eleven of the 24 had sighs in the repeat examinations Of the 11, four had intervening thoracic surgery and one received

*From the Cardio-Pulmonary Laboratory, Veterans Administration Hospital
**Consultant, Pulmonary Physiology
†Chief, Cardio-Pulmonary Laboratory

cortisone for sarcoidosis In these five cases, the results were treated as individual cases but were not used to change the patient count In all other cases of duplicate records on the same individual, the results were averaged This left a total of 86 records that had sighs

Of the six women examined, four (66 7 per cent) had sighs in a total of six records Of the 324 men, 77 (23 8 per cent) had sighs in a total of 87 records Sighing was found in only one of the three normal women and the normal man

Table I shows the distribution of the main diagnoses of the 81 individuals who showed sighing in their respiratory records

The frequency of sighing in the 86 records was as follows 48 (55 8 per cent) sighed once, 19 (22 0 per cent) sighed twice, seven (8 1 per cent) sighed three times, six (7 0 per cent) sighed four times, two (2 3 per cent) sighed 12 times, there was one record (1 2 per cent) each with five, 10 11 and 14 sighs

The individuals ranged in age from 18 to 67 years The average age was 38 3 years Sixty per cent of the individuals were under 40 years old, 29 per cent between 40 and 60 and 10 per cent were over 60 years

A The Sigh and the Vital Capacity[*]

The sigh volume ranged from 760 ml to 3070 ml with an average deflection from the base line of 1690 ml Forty-four per cent of these sighs were under 1600 ml, 49 per cent were between 1600 and 2500 ml, 7 per cent were over 2500 ml (Figure 1)

The observed vital capacity in these individuals ranged from 1360 ml to 5850 ml, with an average of 3490 ml This was on the average 87 per

TABLE I
DISTRIBUTION OF MAIN DIAGNOSIS IN 81 INDIVIDUALS WHO SIGHED

Normal	2
Tuberculosis, pulmonary	40
Tuberculosis plus emphysema	4
Tuberculosis plus bronchogenic carcinoma	1
Tuberculous pericarditis	1
Tuberculous pleurisy	6
Histoplasmosis	1
Coccidioidomycosis	1
Pneumoconiosis	1
Sarcoidosis	5
Hemoptysis, unknown origin	3
Asthma	2
Emphysema	3
Bronchiectasis	3
Bronchogenic carcinoma	1
Arteriosclerotic heart disease	3
Rheumatic heart disease	2
Cor pulmonale	2

[*]The terminology used in this paper is that of Pappenheimer, J R, Chairman, Standardization of Definitions and Symbols in Respiratory Physiology, Fed Proc, 9 602, 1950

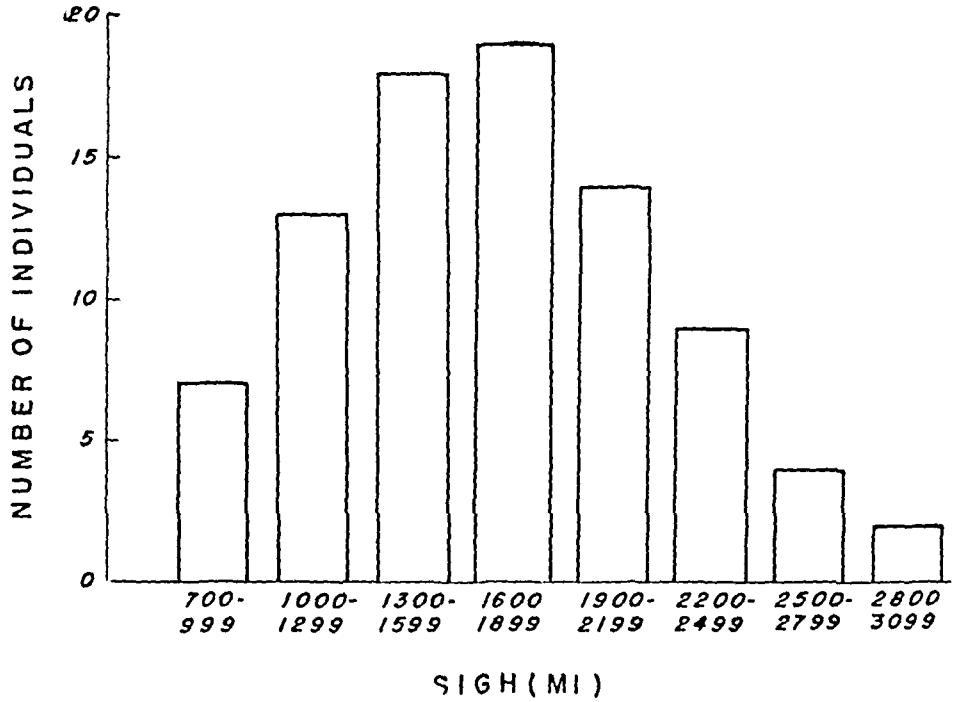


FIGURE 1 Distribution of sigh volume in 86 individuals

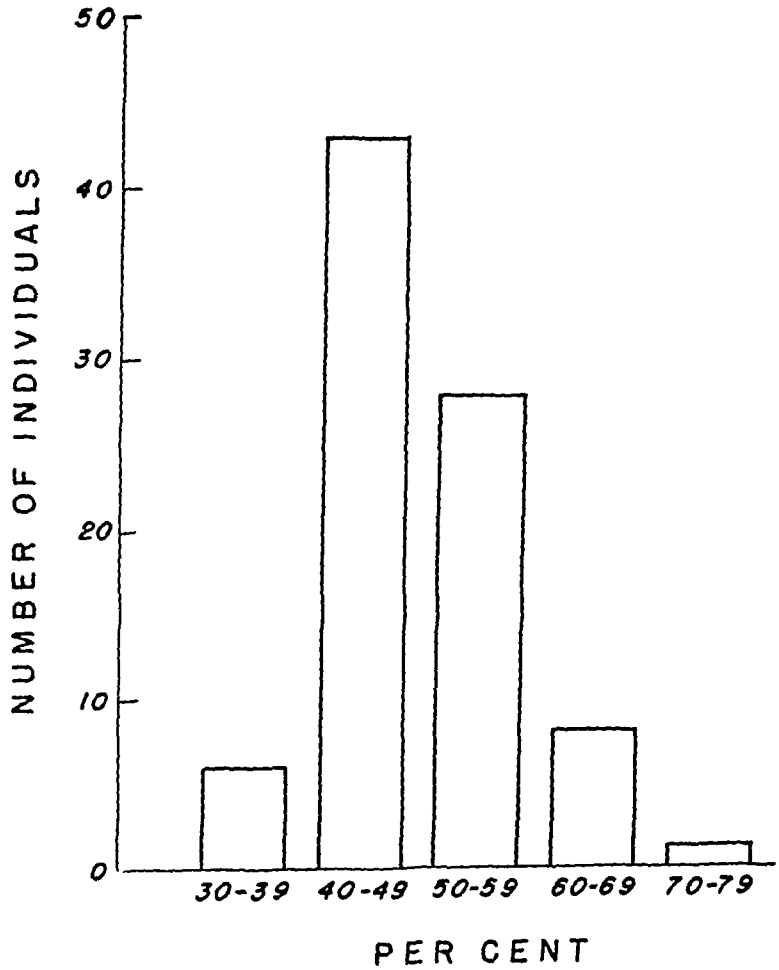


FIGURE 2 Sigh volume in percentage of vital capacity in 86 individuals

cent of the predicted vital capacity Predicted values for vital capacity were based on the regression formula of Baldwin and co-workers [7] The range of the observed vital capacity/predicted vital capacity was from 39 per cent to 134 per cent Twenty nine (33 7 per cent) of the individuals had vital capacities that were under 80 per cent of that predicted, 34 (39 6 per cent) were between 80 and 100 per cent and 23 (26 7 per cent) had vital capacities over 100 per cent of prediction

The sigh ranged from 38 per cent to 70 per cent of the observed vital capacity with a mean of 49 2 per cent (Figure 2) and a mean deviation of ± 5 8 per cent The standard deviation was 7 3

The linear regression of the vital capacity on the sigh was found to be

Vital capacity = 3488 ml + 1 78 (ml of sigh —1690 ml) The coefficient of correlation, r, was found to be + 0 881 Figure 3 shows the scatter diagram with regression line of vital capacity on the sigh

A reduced vital capacity had little effect on the average value for the percentage of the sigh of the observed vital capacity Twenty nine indi-

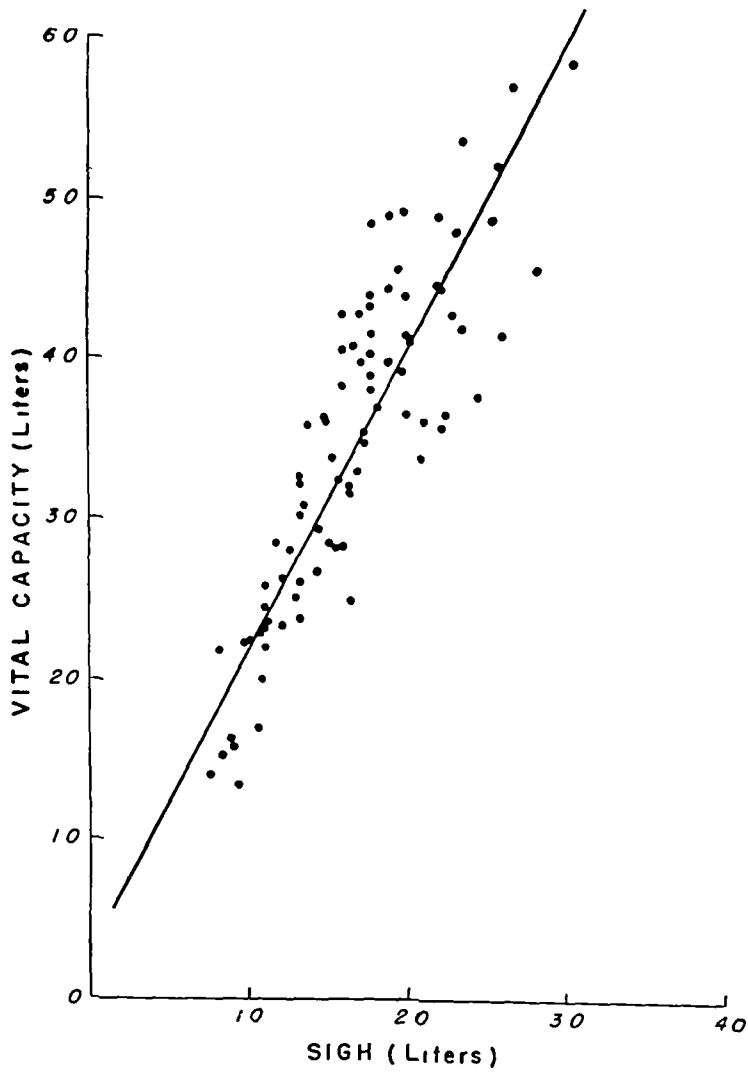


FIGURE 3 Scatter diagram with regression line of vital capacity on sigh

viduals had vital capacities that were under 80 per cent of their predicted vital capacity In these individuals, the average value of their observed vital capacity was 61 per cent of their predicted values and the relationship of the sigh to the observed vital capacity was 52 0 per cent In the 34 individuals who had readings between 80 and 100 per cent of their predicted values the average per cent of observed vital capacity/predicted vital capacity was 91 3 per cent, the sigh was 48 7 per cent of their observed vital capacity In 23 individuals the observed vital capacity was over 100 per cent of their predicted values The average per cent of observed vital capacity/predicted vital capacity was 113 6 per cent In these individuals the relationship, sigh/observed vital capacity, was 46 3 per cent

B The Sigh and the Subdivisions of the Vital Capacity

1 *Tidal volume* The tidal volume ranged between 272 ml and 1115 ml with an average of 557 ml Average values for tidal volume in healthy men under basal conditions are approximately 500 to 600 ml

The mean deflection of the sigh was 310 per cent of the volume of the tidal volume The range was between 160 and 620 per cent of the volume of the tidal volume Three (3 5 per cent) were between 100 and 190 per cent of the deflection of the tidal volume, 37 (43 0 per cent) were between 200 and 290 per cent of the deflection of the tidal volume, 32 (37 2 per cent) were between 300 and 390 per cent of the deflection of the tidal volume, 14 (16 3 per cent) were 400 per cent or more the deflection of the tidal volume (Figure 4)

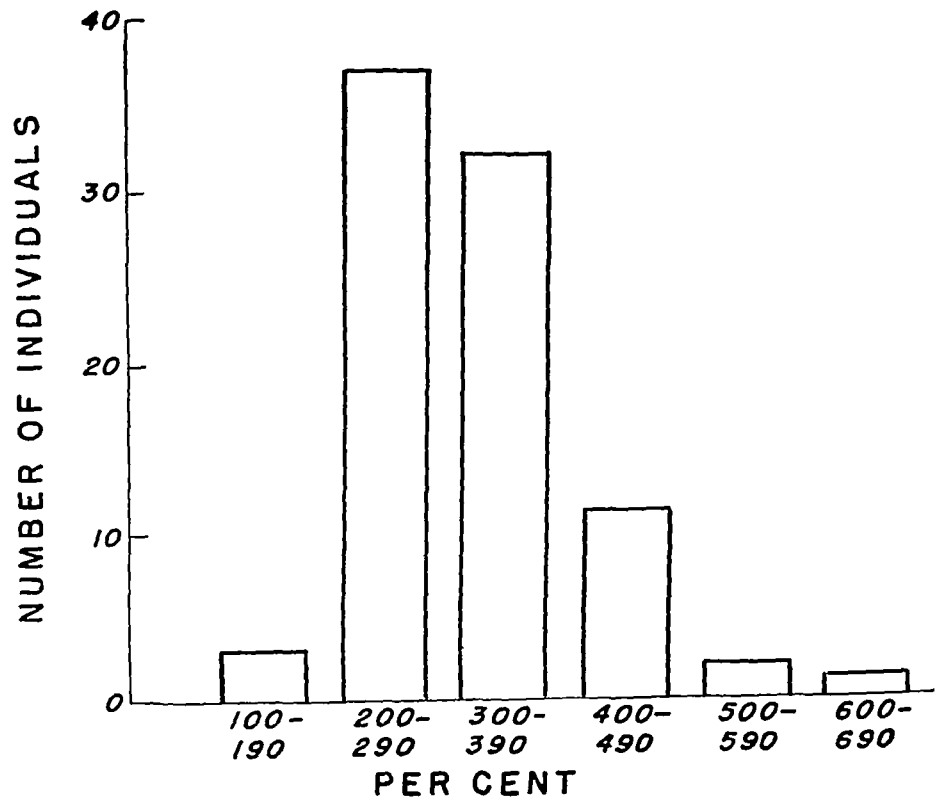


FIGURE 4 Sigh volume in percentage of tidal volume in 86 individuals

In those cases where the sigh was from 100 to 190 per cent of the deflection of the tidal volume, the sigh was 50 7 per cent of the observed vital capacity When the deflection was from 200 to 290 per cent the sigh was 47 9 per cent of the observed vital capacity At 300 to 390 per cent, the sigh was 47 5 per cent of the observed vital capacity At values of 400 per cent and higher, the sigh was equal to 55 7 per cent of the observed vital capacity

2 *Inspiratory capacity* The inspiratory capacity is the maximal amount of air that can be inhaled after normal expiration It equals tidal volume plus inspiratory reserve volume

The inspiratory capacity ranged from 1021 ml to 4415 ml, with a mean of 2648 ml

The sigh ranged from 44 per cent to 90 per cent of the inspiratory capacity with a mean of 65 1 per cent The distribution is shown in Figure 5

The linear regression of the inspiratory capacity on the sigh was found to be

Inspiratory Capacity =2648 ml + 1 34 (ml of sigh —1690 ml) The coefficient of correlation, r, was found to be +0 836 Figure 6 shows the scatter diagram with regression line of inspiratory capacity on the sigh

3 *Inspiratory reserve volume* The inspiratory reserve volume is the maximal amount of air that can be inspired from the end-inspiratory position following a quiet inspiration, it is measured from the resting end-inspiratory level It equals inspiratory capacity minus tidal volume

The inspiratory reserve volume ranged from 690 ml to 3763 ml, with a mean of 2080 ml

The inspiratory reserve portion of the sigh was found to range from 33 per cent to 90 per cent of the inspiratory reserve volume itself, with a mean of 55 4 per cent (Figure 7)

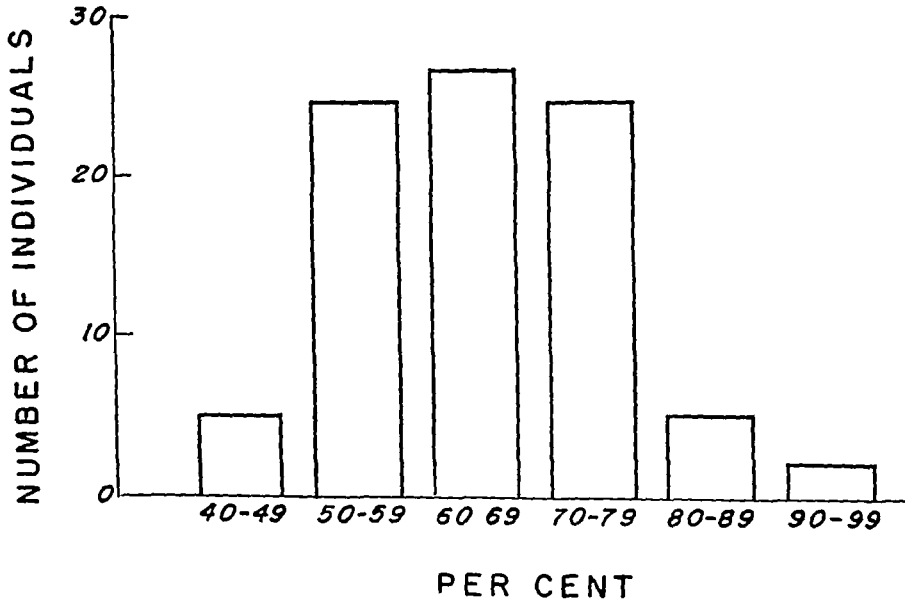


FIGURE 5 Sigh volume in percentage of inspiratory capacity in 86 individuals

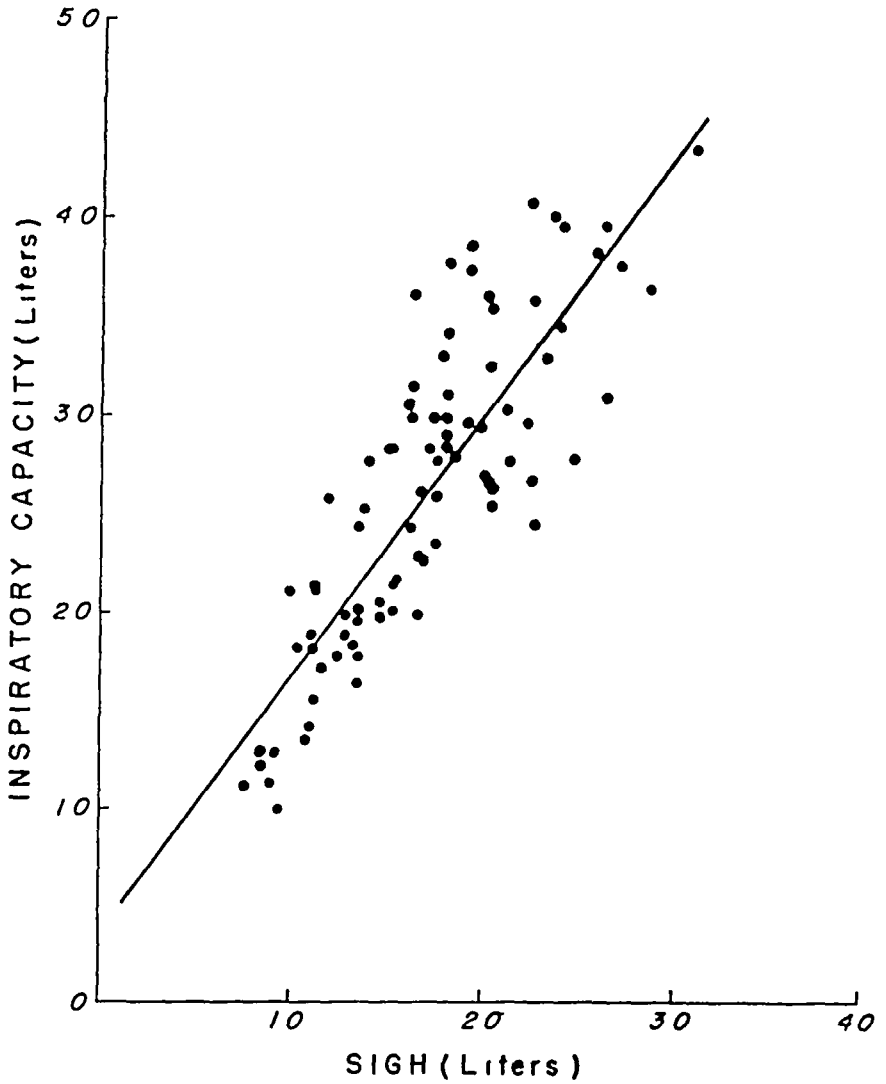


FIGURE 6 Scatter diagram with regression line of inspiratory capacity on sigh

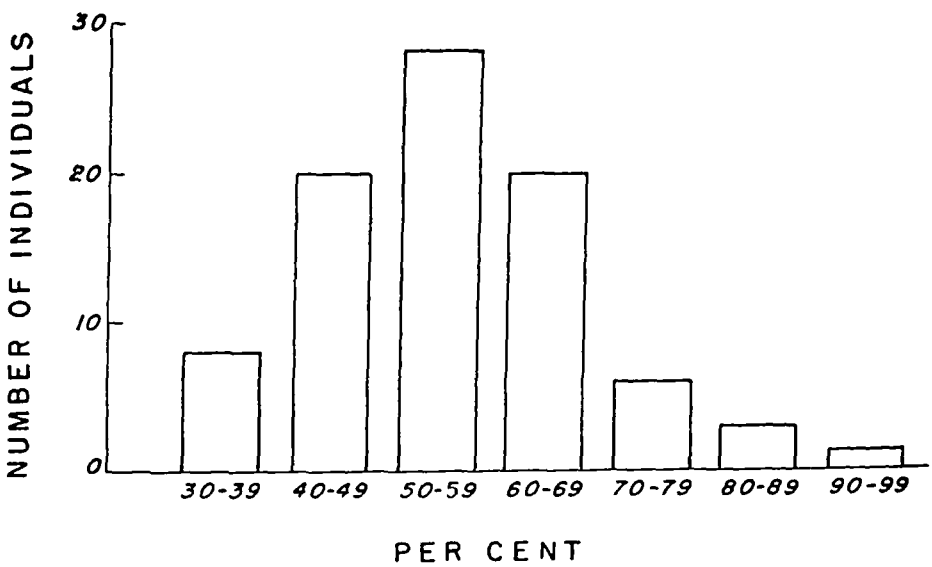


FIGURE 7 Sigh volume minus tidal volume in percentage of inspiratory reserve volume in 86 individuals

C The Sigh and Ventilation

1 *Tidal volume* This has been discussed under the relationship of the sigh to subdivisions of the vital capacity

2 *Frequency of respirations* The number of respirations was six to 24 per minute, the mean being 13 8

Of the 86 individuals who produced sighs, 11 (12 8 per cent) had respirations under 10 times per minute, 42 (48 8 per cent) from 10 to 14 times, 25 (29 1 per cent) between 15 and 19 times and eight (9 3 per cent) from 20 to 24 times per minute

In all groups the sighing volume was of about the same percentage of the observed vital capacity (47 8 to 51 4 per cent)

3 *Ventilation equivalent* Ventilation equivalent is defined as the amount of ventilation required for 100 ml of oxygen uptake Normally, this is from two to three liters This is essentially a measure of efficiency of pulmonary circulation The ventilation equivalent ranged from 1 7 to 4 9 liters, with a mean of 2 86 liters

Sixty-three per cent had ventilation equivalents of 3 0 and lower, 37 per cent were 3 1 and higher In the 54 individuals whose ventilation equivalent was 3 0 and lower the sigh was 48 8 per cent of the observed vital capacity and in the 32 individuals whose ventilation equivalent was 3 1 and higher the sigh was 49 8 per cent of the observed vital capacity

D The Sigh in Oxygen and Air Breathing

Another series of 340 records (mostly of patients with pulmonary tuberculosis) of breathing air for six minutes followed by a six minute period of oxygen breathing were examined for the presence of sighs In 30 sighs occurred only when breathing air, in 17, only when breathing oxygen, and in 50 cases sighs were seen during air breathing and oxygen breathing The occurrence of sighing is, therefore, not significantly diminished by oxygen, moreover, in a considerable number of cases it occurs on breathing oxygen only

It has been shown,[8] that the number of sighs increases under re-breathing or carbon dioxide breathing, when sighing is normally present If sighing is not normally present, it usually does not appear under these experimental conditions

E The Sigh in Bronchospirometric Recordings

The bronchospirometric recordings of 74 patients were examined for sighs In six they were found in bronchospirometric as well as in the spirometric records

Table II shows the relation of the sigh of the right lung to the total sigh At an average it is 50 per cent On the same table the vital capacity of the right lung in per cent of the total vital capacity is given, the average is 47 per cent The relative sigh volume of one lung in relation to that of both lungs is parallel to the relative volume of the vital capacity of the respective lung

TABLE II—THE SIGH IN BRONCHOSPIROMETRY

Patient	VC, Broncho-spirometry X 100 / VC, Spirometry	Right Lung	
		Vital Capacity Per Cent of Total	Sigh Per Cent of Total
1	90	29	37
2	96	37	45
3	88	34	32
4	97	47	50
5	91	78	76
6	84	55	60
Average	91	47	50

On bronchospirometry, the sigh (right + left) was found to be from 82 to 125 per cent of the sigh as found on spirometry, with a mean of 102 per cent At the same time the vital capacity on bronchospirometry (right + left) was found to range from 84 to 97 per cent of the vital capacity as determined on spirometry, with a mean of 91 per cent

II The Sigh in Neurological Cases

Twenty graphic records of respiration of 11 patients of the Neurological Service were also examined for the presence of sighs Fifteen records of eight patients showed sighing Four records of two patients showed the type of sigh discussed above Eleven records of six patients showed a different type of sigh In these eleven records *the sigh was greater in volume than the voluntary vital capacity* The reflex action involved in the sigh moved more air in and out of the lungs than the patient could do voluntarily In all other patients the sigh volume was always smaller than the vital capacity

The frequency of sighing in the records of the six neurological patients who showed sighs larger in volume than their vital capacity was as follows Three sighed once and three twice This lack of a greater frequency of sighing in the records of the neurological patients would appear to rule out a reflex adaptive mechanism to increase diminished respiration

Of the two neurological patients who showed the typical sigh, one had a Guillain Barré syndrome and the other a basilar artery thrombosis Of the six patients who showed sighs that were greater than their voluntary vital capacity, one had a brain injury of the right temporal area (gun shot), one had an ependymoma of the upper cervical cord, one had paralysis agitans, two had multiple sclerosis, and one had neurofibromatosis

The following case histories give the pertinent data in four cases

Case 1 R J D This 32 year old white man, gave a history of having developed subcutaneous manifestations of neurofibromatosis between 1942 and 1945 In 1950 he began to have neurological symptoms in the left upper extremity, which became progressively more severe and extensive Diagnosis of a cervical cord involvement was made following laminectomy in February, 1951 Since that time he has had three laminectomies Extensive involvement of the cord at C-2 by tumor was noted At present he has progressed to tetraplegia The deep tendon reflexes have always been hyperactive

The following is a record of his vital capacities and sighs

	Vital Capacity	Involuntary Sigh
8-23-54	720 ml	1050 ml
9-15-54	900 ml	1400 ml
11- 9-54	930 ml	1450 ml
1- 2-55	810 ml	1290 ml
4-19-55	830 ml	1190 ml
6-13-56	560 ml	1270 ml

In each instance his involuntary sigh is larger than his voluntary vital capacity

Case 2 R R This 30 year old white man, was in good health until July, 1953 when he experienced weakness and fatigue in his legs He is now unable to walk, has difficulty in swallowing, his eyesight is impaired, he has loss of urinary control and no longer has spontaneous bowel movement He has considerable muscular dystrophy and loss of deep tendon reflexes His present diagnoses (1) Multiple sclerosis, severe (2) Paraplegia, spastic (3) Paralysis of bladder, flaccid

	Vital Capacity	Involuntary Sigh
August 26, 1954	700 ml	1940 ml

Graphs of the involuntary sigh and the voluntary vital capacity are shown in Figure 8

Case 3 H G S This 26 year old white man, sustained a penetrating wound of the right temporal area of the skull on March 17, 1953 Right temporal craniotomy was performed and the wound and missile tract debrided Examination at time of respiratory studies showed, (1) Wound, penetrating, of right temporal region of brain (2) Encephalomalacia of brain stem, upper part, due to trauma (3) Quadriplegia, with hyperactive deep tendon reflexes

	Vital Capacity	Involuntary Sigh
January 3, 1956	1410 ml	3365 ml

Case 4 M J This 73 year old white woman, was in good health until 1949, when she experienced pain at the back of her neck The pain continued and became progressively more severe Early in 1952, she began to experience weakness in the extremities on the right side She entered the hospital and a diagnosis of a cord tumor was made An operation for removal of the tumor from the cervical cord was performed in April, 1952 She now has a quadriplegia and is confined to bed Her diagnosis is (1) Ependymoma, upper cervical cord, post operative status (2) Quadriplegia, with hyperactive deep tendon reflexes

	Vital Capacity	Involuntary Sigh
April 13, 1956	380 ml	715 ml

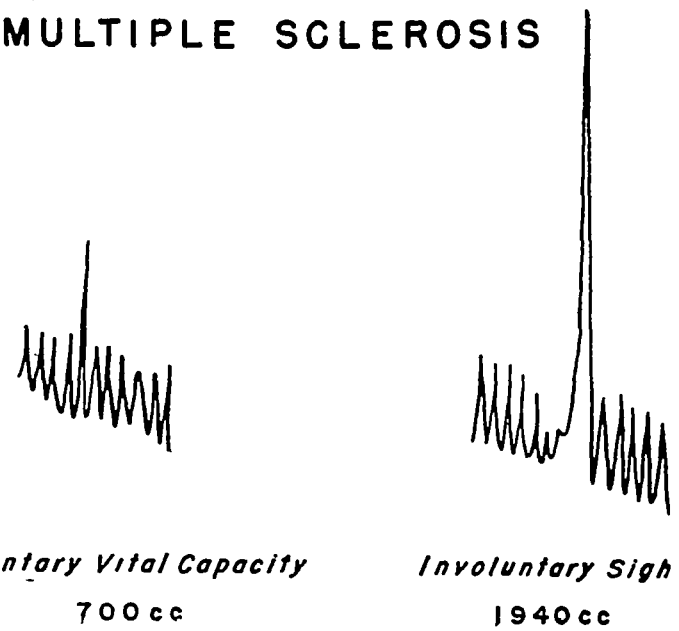


FIGURE 8 Voluntary vital capacity and involuntary sigh in patient with multiple sclerosis

Discussion

Sighing, which is a deep inspiration, is usually described as a sign of neurocirculatory asthenia[1] and is common in neurotics[9] However, it occurs in many healthy as well as sick individuals Sighing respiration was seen in the spirograms of 81 of 330 individuals who, when undergoing pulmonary function tests, were breathing oxygen for two 6-minute periods Among these were healthy people and patients with various forms of pulmonary and cardiac diseases, in all age groups

When the volume of the sigh is compared with the vital capacity in the same subject, a direct correlation can be found between these two measurements A larger vital capacity permits a larger sigh, a diminished vital capacity causes diminution of the sigh A similar correlation exists between inspiratory capacity and sigh The tidal volume, however, does not affect the size of the sigh In our observations the sighs ranged from 160 to 620 per cent of the tidal volume Neither did the rate of respiration or ventilation equivalent show any relation to the size of the sigh

Sighing respiration may occur while breathing air as well as while breathing oxygen Most of our patients whose spirograms were recorded with air and oxygen inhalation produced sighs under either condition In a minority, sighing was observed when either breathing air or when breathing oxygen

Bronchospirometric examinations, in spite of local anesthesia, excitement, trauma, stenosis breathing, does not abolish the sighing respiration

The volume of the sigh is, as expected, usually smaller than the vital capacity of the same individual, However, to our greatest surprise, we observed the opposite in six patients with various neurological involvements In these patients the involuntary sigh was greater—sometimes considerably greater, than the vital capacity These patients had as different diseases as Brain injury of the right temporal area, ependymoma of the upper cervical cord, paralysis agitans, multiple sclerosis, neurofibromatosis All these patients had low vital capacities

Sighing is considered to be a reflex, and the intensity of this reflex was apparently increased in this group of patients However, the lack of a greater frequency of sighing in the records of the neurological patients would appear to rule out a reflex adaptive mechanism to increase diminished respiration If we compare it with the deep tendon reflexes, there did not seem to be a correlation Although four of these six patients had hyperactive deep tendon reflexes, normal reflexes were found in one and loss of deep tendon reflexes was found in one

Sighing disappears during sleep and therefore, is believed to be of cortical origin[10] It is sensitive to voluntary control and to the emotions[11] Induced unpleasant ideas increase the number of sighs[9] However, in experiments in dogs sighing respiration was demonstrated in medullary preparations "The rhythm of the sighing type of breathing is more pronounced in midcollicular and pontine preparations and is enhanced by vagotomy At all levels, but particularly at the midcollicular and pontine

levels, there is pronounced inhibition of eupnea by the sighing respiration This occurs after vagotomy and is thus not dependent upon pulmonary reflexes initiated by the deep breath "[12]

Sighing respiration can be produced in dogs by morphine [13] None of our patients had received morphine prior to the recording of their respiration and morphine plays no role in our observations

Whalen[2] states "Since sighing has been revealed in experimental animals only after transection of the brain stem and vagotomy, or after severe hypoxia in intact animals, the cause of the sighing seen in the present experiments is an enigma" Similarly we may say from our own observations The cause of the large volume of the sigh in our six neurological patients as compared with their voluntary vital capacity is an enigma

SUMMARY

A sigh is defined as a deep inspiration, 1 5 times or more of the tidal volume

In 417 spirograms of 330 individuals (normals and patients with various pulmonary and cardiac diseases) taken during two six minute periods of oxygen breathing, 93 spirograms of 81 individuals showed sighs

Patients with larger vital capacities produced larger sighs than those with smaller vital capacities A similar parallelism existed between inspiratory capacity and sigh volume No correlation was found between tidal volume and sigh volume

In another series of studies it was seen that sighs occur under air breathing as well as under oxygen breathing

Sighing respiration could also be recorded during bronchospirometric studies

Six patients with various neurological disorders produced sighs greater in volume than their vital capacities The sigh is apparently caused by a reflex which was not disturbed in these patients in whom the pathway for a voluntary deep breath had been damaged

RESUMEN

Se define un suspiro como una inspiración profunda, 1 5 veces o más que el aire corriente

En 417 espirogramas de 330 individuos (normales y enfermos de varias afecciones pulmonares y cardiacas) tomados durante dos períodos de seis minutos de respirar oxígeno, se encontraron 93 suspiros de 81 individuos

Los enfermos con mayor capacidad vital produjeron más amplios suspiros que aquéllos con pequeñas capacidades vitales Existe un paralelismo semejante entre la capacidad inspiratoria y el volumen del suspiro No se encontró correlación entre el aire corriente y el volumen del suspiro

En otra serie de estudios se ha visto que el suspiro ocurre al respirar aire lo mismo que al respirar oxígeno

La respiración suspirosa puede también observarse durante los estudios broncoespirométricos

En seis enfermos con varios trastornos neurológicos se produjeron suspiros mayores en volumen que sus capacidades vitales

El suspiro es causado aparentemente por un reflejo que no fué perturbado en aquellos enfermos en quienes la vía para producir una respiración profunda voluntaria ha sido danado

ZUSAMMENFASSUNG

Ein Seufzer wird definiert als eine tiefe Inspiration, 1,5 mal oder mehr des Atemvolumens umfassend Von 417 Spirogrammen von 330 Personen (Gesunde und Kranke mit verschiedenen Lungen- und Herzkrankheiten) aufgenommen während 2 Sechsminuten-Perioden unter Sauerstoffatmung, zeigten 93 Spirogramme von 81 Personen Seufzer

Patienten mit höherer Vitalkapazität hatten stärkere Seufzer als solche mit geringerer Vitalkapazität Eine ähnliche Parallelle bestand zwischen Einatmungsluft und Seufzervolumen Eine Korrelation wurde nicht gefunden zwischen Atemvolumen und Seufzervolumen

Einer anderen Untersuchungsreihe war zu entnehmen, dass Seufzer vorkommen sowohl bei Luftatmung wie bei Sauerstoffatmung

Seufzeratmung konnte ferner im Verlauf von Bronchospirometrischen Untersuchungen aufgenommen werden

6 Patienten mit verschiedenartigen neurologischen-Störungen hatten Seufzer, deren Volumina grösser waren als ihre Vitalkapazität Der Seufzer entsteht wahrscheinlich durch einen Reflex, der nicht unterbrochen ist bei solchen Patienten, bei denen die Leitung für eine willkürliche vertiefte Atmung gestört ist

Acknowledgment The writers gratefully acknowledge the cooperation of Dr W O Howard, Chief, Neurology Section, and the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey

REFERENCES

1 *Webster's New International Dictionary of the English Language*, 2nd Edition, Merriam Company, Springfield, Mass , 1952
2 Whalen, W J "Some Effects of Hyperventilation on Respiratory Patterns," *Am. J Physiol*, 183 445, 1955
3 Rechnitzer, E , Rosenbluth, E and Wassermann, S "Über nervose Atemstörungen," *Ztschr f klin Med*, 109 613, 1929
4 White, P D and Hahn, R G "The Symptom of Sighing in Cardiovascular Diagnosis, with Spirographic Observations," *Am J Med Sciences*, 177 179, 1929
5 Gallavardin Les Angines de Poitrine, Paris, 1925, p 100, quoted by Baker, M "Sighing Respiration as Symptom," *Lancet*, 1 174, 1934
6 Caughey, J L , Jr "Analysis of Breathing Patterns," *Am Rev Tuberc*, 48 382, 1943
7 Baldwin, E deF , Courand, A and Richards, D W , Jr "Pulmonary Insufficiency, I Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects," *Medicine*, 27 243, 1948
8 Cobb, S and Cohen, M E "Experimental Production During Rebreathing of Sighing Respiration and Symptoms Resembling Those in Anxiety Attacks in Patients with Anxiety Neurosis," *J Clin Invest*, 19 789, 1940
9 Finesinger, J E "The Spirogram in Certain Psychiatric Disorders," *Am. J Psychiatry*, 100 159, 1943
10 Altschule, M D *Bodily Physiology in Mental and Emotional Disorders*, Grune and Stratton, New York, 1953
11 Christie, R V "Some Types of Respiration in Neurosis," *Quarterly J Med*, 4 427, 1935
12 Hoff, H E and Breckenridge, C G "Levels of Integration of Respiratory Patterns," *J Neurophysiol*, 15 47, 1952
13 Breckenridge, C G and Hoff, H E "Influence of Morphine on Respiratory Patterns," *J Neurophysiol*, 15 57, 1952

SECTION ON CARDIOVASCULAR DISEASES

Proximal Interruption of a Pulmonary Arch (Absence of One Pulmonary Artery) Case Report and a New Embryologic Interpretation

RAY C ANDERSON, PH D, M D, FLORENCE CHAR, M D
and PAUL ADAMS, JR, M D, F C C P
Minneapolis, Minnesota

Congenital absence of the right or left pulmonary artery is a rare anomaly, with less than 50 cases in the medical literature Although Frantzel[1] is generally credited with having described the first case of this type, his case was atypical, since it involved an "aortic-pulmonic" defect and had a right pulmonary artery arising from the ascending aorta This pulmonary artery was probably an "ectopic" pulmonary artery, resulting from abnormal aortic-pulmonic septum formation, and not an "absent pulmonary artery" in the usual sense The first typical autopsied case to be reported was that by Doring[2] Subsequent cases have been diagnosed at autopsy[3-6] and at operation[7,8] Madoff, et al,[9] in their review of the subject in 1952, were the first to report the successful clinical diagnosis of this condition, utilizing angiocardiography Since then, numerous authors[10-19] have reported cases similarly diagnosed Cardiorespiratory data were included in some of these case reports[9,11,1] To the best of our knowledge, no published case has had proved pulmonary hypertension The following case report is therefore unique in this regard

Case Report

B P (U H 887346), a male infant, was born on February 11, 1955, following an uncomplicated, full term pregnancy Delivery was spontaneous and normal The birth weight was 4225 grams There was no neonatal complication, although from birth he was noted to have deep but not labored respirations At the age of seven weeks he had the first bout of "pneumonia," characterized by low grade fever and rapid respirations He was treated at home with intramuscular penicillin, with apparent recovery in a few days During subsequent months the infant had two similar episodes and was again treated at home

Between the ages of four and six months, he had two rather severe bouts of pneumonia, both of which required hospitalization Cardiomegaly was first noted at the age of five months, together with circumoral cyanosis on exertion and crying Because of the repeated bouts of pneumonia and enlarging heart size, he was referred to University Hospitals on August 10, 1955, for further evaluation Growth and development up to this time had been normal

From the Department of Pediatrics, University of Minnesota Dr Char was a Trainee in Cardiology, National Heart Institute, United States Public Health Service This study was aided by a grant from the Minnesota Heart Association

On physical examination the infant was noted to have slight tachypnea and mild circumoral cyanosis His weight was 7800 grams and his length was 70 centimeters A few moist rales were heard in both lungs The heart was enlarged to percussion A grade 1 systolic murmur was heard best in the fourth and fifth left intercostal spaces along the left sternal border and the pulmonic second sound was noted to be slightly accentuated The liver was palpable just below the right costal margin The electrocardiogram showed right axis deviation, right ventricular preponderance greater than normal for age, and abnormally peaked P waves Roentgenographic studies showed a moderately enlarged heart with prominence of the pulmonary artery segment and the right ventricle The pulmonary vascular markings in the left lung appeared increased but those in the right lung appeared decreased (Figure 1) An angiocardiogram showed absence of filling of the right pulmonary artery (Figure 2) He responded well to digitalization and was therefore discharged on September 11, 1955

He was readmitted three weeks later because of dyspnea, circumoral cyanosis, and pulmonary congestion He improved with antibiotic therapy Because of the known occurrence of associated cardiac malformations in patients with absence of a pulmonary artery, cardiac catheterization was done on October 10, 1955 The findings suggested a patent ductus arteriosus (Table I), so a retrograde aortogram was done the following day in an attempt to better identify such a defect This study demonstrated multiple fine collateral vessels arising from the aorta and passing to the right chest, as well as a larger vessel arising from the left subclavian artery and crossing over to the right chest (Figure 3) No patent ductus arteriosus was demonstrated

The patient was discharged from the hospital on October 24, 1955, but subsequently required repeated hospitalizations because of severe dyspnea and cyanosis He failed to gain weight and his cardiac status gradually worsened Auricular fibrillation and flutter developed A repeat angiocardiogram was performed in the antero-posterior view, to check for a possible localized obstruction of the right pulmonary artery Again, there appeared to be complete absence of the right pulmonary artery (Figure 4) Because his condition was deteriorating rapidly, a repeat cardiac catheterization was done

FIGURE 1

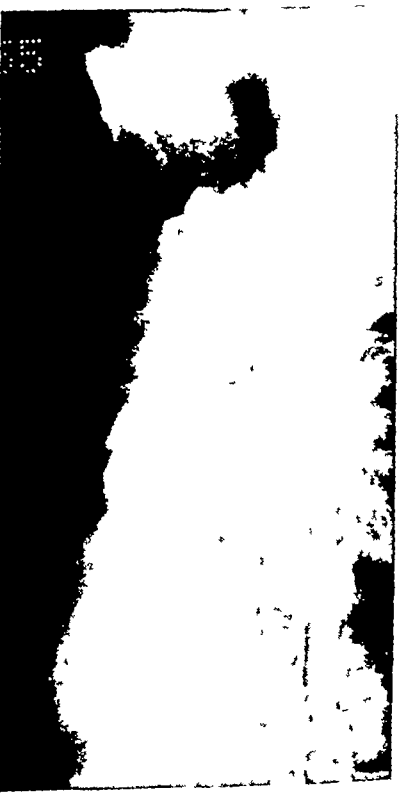


FIGURE 2

Figure 1 Roentgenogram of the chest (antero-posterior view), demonstrating cardiomegaly, prominent main pulmonary artery segment, and decreased pulmonary vasculature on the right side.—*Figure 2* Angiocardiogram (right posterior oblique view), demonstrating absence of the right pulmonary artery

TABLE I

CARDIAC CATHETERIZATION DATA

	Age 8 Months—Oct 10, 1955			Age 13 Months—March 9, 1956		
	Pressure In Mm Hg	Oxygen Content In Volumes/100 cc (Van Slyke)	Per Cent Oxygen Saturation	Pressure In Mm Hg	Oxygen Content In Volumes/100 cc (Van Slyke)	Per Cent Oxygen Saturation
Pulmonary artery	56/20 Mean 33	9 14	56 63	110/80 Mean 90	5 40	40 54
Right ventricle	56/0	7 27	45 04	110/0	5 46	40 99
Right atrium		8 03	49 75		5 93	44 52
Inferior vena cava		7 99	49 50		4 59	34 59
Superior vena cava		7 40	45 85		4 74	35 59
Femoral artery		15 56	94 55		11 02	80 48

Total Pulmonary Resistance Oct 10, 1955—2585 dynes sec cm $^{-5}$
March 9, 1956—6200 dynes sec cm $^{-5}$

on March 9, 1956, in the hope of revealing a correctable intracardiac defect This study showed a further marked increase in pulmonary artery pressure but no left to right shunt (Table I)

He was admitted to the hospital for the last time on April 4, 1956, with marked cardiomegaly and severe congestive failure He died two days later

Autopsy findings There was complete symphysis pleurae on the right side The heart was markedly enlarged, particularly the right ventricle The valves and endocardium were normal The ventricular septum was intact and the foramen ovale was closed The great vessels arose in the usual manner but the main pulmonary artery gave rise only to an enlarged left pulmonary artery (Figure 5) The coronary vessels and pulmonary veins were normal A ductus arteriosus, measuring 1 5 millimeters in diameter, connected with the left pulmonary artery but not patent An obliterated vessel, measuring 1 5 millimeters in diameter (probably a right ductus arteriosus) arose from the proximal portion of the innominate artery and passed to the hilum of the right lung At the hilum this vessel joined a widely patent vessel 4 millimeters in diameter which then branched to supply the various lobes of the lung The branch of the left subclavian artery demonstrated by aortography was not identified, and apparently supplied the surface of the lung rather than the hilum The left lung was firm and had lost its crepitance On cut section, this lung exuded large amounts of bloody froth The right lung was smaller than the left and had several areas of congestion and atelectasis Sections of both lungs were examined microscopically by Dr Donald F Ferguson of the Veterans Administration Hospital, Minneapolis, Minnesota A Verhoeff-Van Gieson elastic stain was used The left lung showed severe

medial hypertrophy of the small arteries but no intimal proliferation was noted in any vessels less than 150 microns in diameter The veins and capillaries appeared normal (Figure 6) Sections from the right lung were strikingly different The pulmonary arteries in this lung had very thick and dense adventitia, and seemed rather small in comparison to the adjacent bronchi The smaller arterioles, so prominent in the left lung, were hardly distinguishable There was no evidence of medial or intimal lesions in the pulmonary arterial vessels in the right lung (Figure 7) The veins and capillaries were normal

Discussion

Embryologic Features

Among published cases of absent left or right pulmonary artery there is a preponderance of the former The former tends to be associated with an intracardiac defect, particularly tetralogy of Fallot, while absence of the right pulmonary artery generally occurs as an isolated finding[18 20] There have been at least five cases of absent right pulmonary artery described with an associated patent ductus arteriosus,[1 2 4 11 19] and in two of these there was also a coarctation of the aorta

McKim and Wigglesworth[15] reviewed the embryologic aspects of this defect in considerable detail, and emphasized that the aortic arch is usually on the side opposite to the absent pulmonary artery Thus, absent left

FIGURE 3

FIGURE 4

Figure 3 Retrograde aortogram (antero-posterior view), demonstrating bronchial arteries and an anomalous branch from the left subclavian artery passing to the right chest —*Figure 4* Angiocardiogram (antero-posterior view), demonstrating absence of the right pulmonary artery

pulmonary artery often occurs in tetralogy of Fallot having a right aortic arch These authors described an anomalous vessel running from the innominate artery to the left lung hilum in three cases with right aortic arches and interpreted this vessel as an obliterated left ductus arteriosus They considered that the heart end (the ventral portion of the sixth arch) of the left pulmonary artery had disappeared, while the ductus arteriosus (the dorsal portion of the sixth arch) had remained in continuity with the distal portion of the left pulmonary artery, first as a functioning vessel and later as a fibrotic non-patent structure McKim and Wiglesworth also suggested that the aortic bud (dorsal portion of the sixth arch) may have grown directly into the pulmonary plexus without there having been a pulmonary artery *per se*, but considered this a less likely possibility in view of the normal anatomical development of the hilar and intrapulmonary arteries in these cases

Emanuel and Pattinson[20] called attention to the presence of developmental defects of the bulbis cordis (as in tetralogy of Fallot) in cases

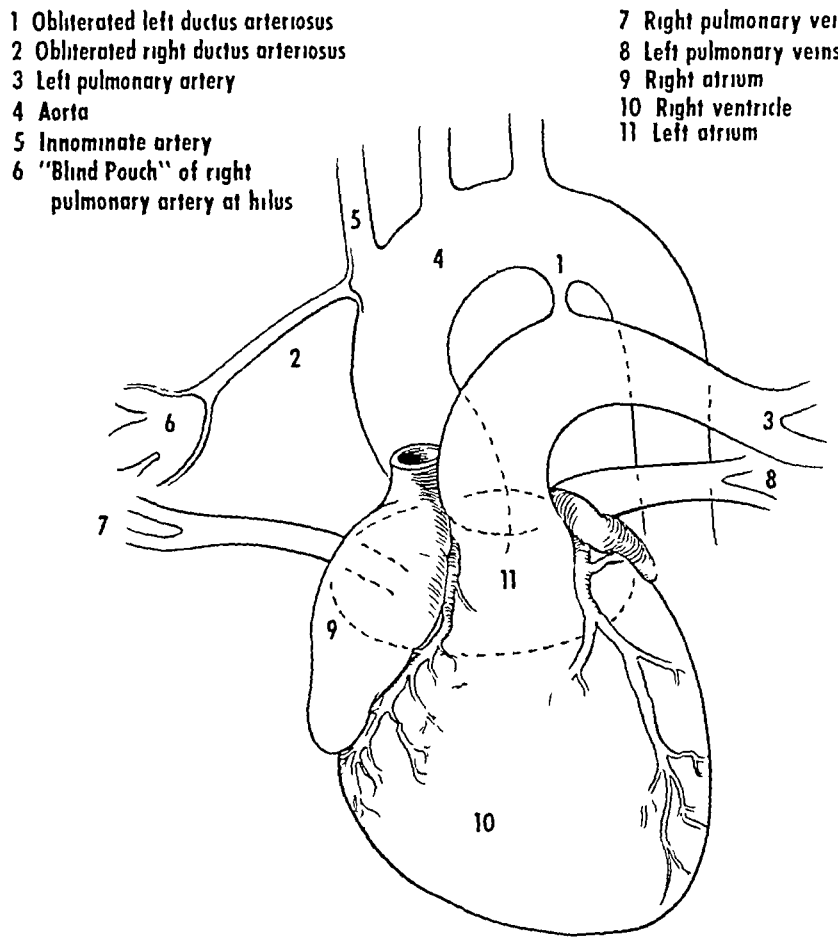


FIGURE 5 Drawing of autopsy specimen, showing connection of right ductus arteriosus (obliterated lumen) to right pulmonary artery

where a left pulmonary artery is absent, and attributed the latter to faulty absorption of the left sixth arch They stated that if the conventional view of symmetrical development of the two pulmonary arteries is accepted, the foregoing association could not be explained They pointed out that this still did not explain the association of absent right pulmonary artery with normal intracardiac anatomy, though they suggested that in such cases perhaps the proximal portion of the right sixth arch became involved in the normal absorption of the left sixth arch

To us, the observations and interpretations of both the foregoing groups, as well as those of the embryologists, Bremer[21] and Congdon,[22] can best be brought together as follows The aortic (fourth) arches begin symmetrically, but unilateral dominance develops rapidly Similarly, the sixth arches begin symmetrically, but deviate at about the time that the arterial trunk is becoming divided (Figure 8a) The dorsal or ductal portion (B) of the pulmonary arch on the side opposite to the dominant pulmonary arch (carrying the greater blood flow) normally undergoes degeneration This allows a straightening out of the pulmonary artery on this side, and also combines with the action of the increasing blood current to permit the pulmonary trunk and other pulmonary arch to align The result in the normal individual is that the main pulmonary artery is derived from the pulmonary trunk and some of the proximal portion (A) of the left pulmonary arch, the left pulmonary artery consists of

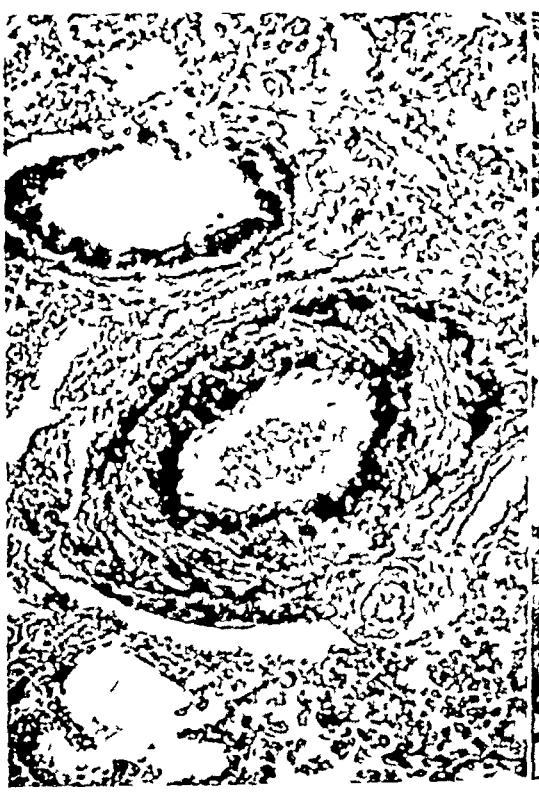


FIGURE 6

FIGURE 7

Figure 6 Photomicrograph of small artery from left lung, demonstrating marked medial hypertrophy.—*Figure 7* Photomicrograph of small artery from right lung, demonstrating normal arteriolar wall and thick adventitia

the primitive left pulmonary artery, and the right pulmonary artery consists of the primitive right pulmonary artery plus a portion (D) of the right pulmonary arch (Figure 8c) Thus there is definite asymmetrical

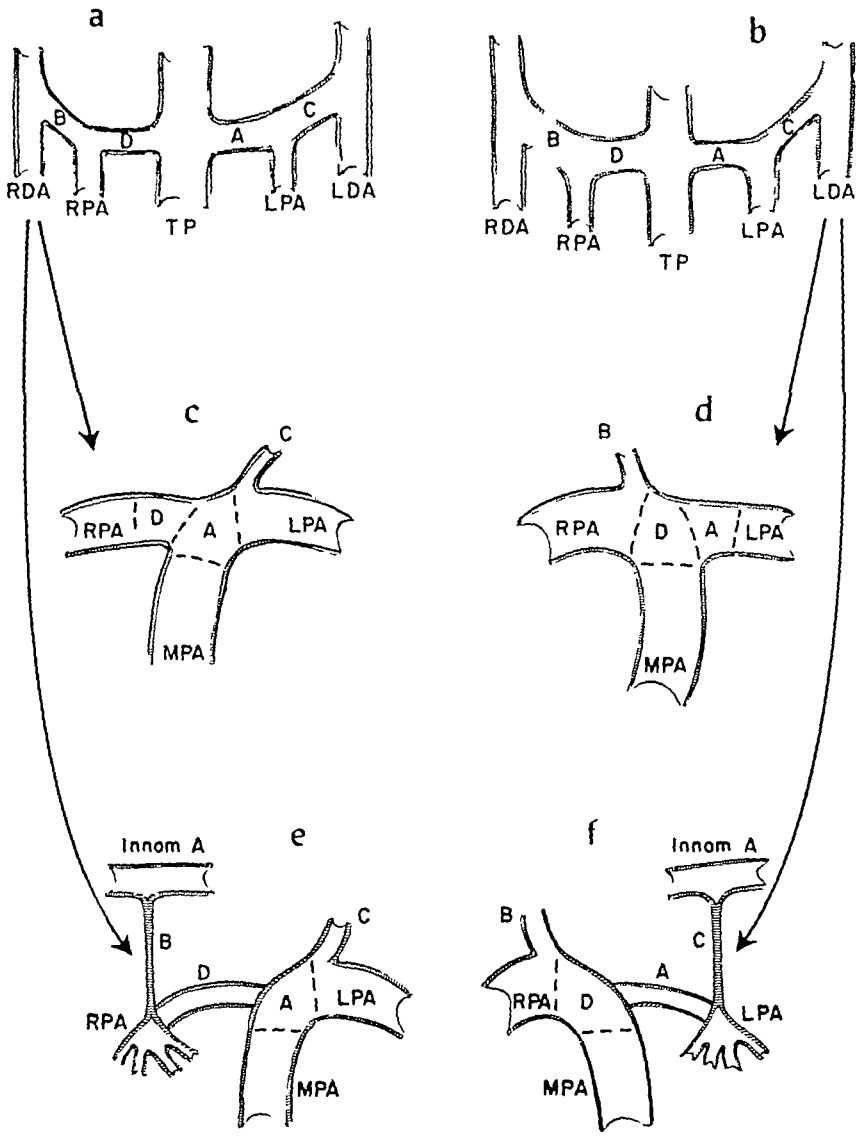


FIGURE 8 a Schematic diagram of pulmonary arch system at early stage of normal development The terminology of Emanuel and Pattinson[9] has been followed for ease of comparison Proximal (ventral) portion of pulmonary arch designated as "A" on left and "D" on right, and distal (dorsal or ductal) portion designated as "C" on left and "B" on right Left and right primitive pulmonary arteries designated as "LPA" and "RPA" Pulmonary trunk indicated by "TP," and left and right descending aortae, by "LDA" and "RDA" b Comparable diagram in case where the right pulmonary arch becomes dominant c Standard adult pattern of pulmonary vessels, with embryologic derivatives indicated "MPA" indicates main pulmonary artery d Comparable adult pattern where right pulmonary arch was dominant e Adult pattern in case of absent right pulmonary artery The left ductus arteriosus (shown as being patent here) indicated by "C," the right ductus arteriosus (shown as being obliterated) indicated by "B," and the underlying arch defect (interruption) indicated by "D" f Adult pattern in case of absent left pulmonary artery The right ductus arteriosus (shown here as being patent) indicated by "B," the left ductus arteriosus (shown here as being obliterated) indicated by "C," and the underlying arch defect (interruption) indicated by "A"

development of the definitive pulmonary arteries The direction of asymmetry is probably dependent primarily on the characteristics of the aortic sac and anterior arches, the fourth in particular (which determines the location of the definitive aortic arch) Blood flow is certainly involved in this deviation in symmetry, but it is difficult to distinguish cause from effect in this regard It is well to remember that the normal interruption of the right pulmonary arch (ductal portion of B) takes place prior to the normal interruption of the right fourth arch

One can theorize that if the dorsal portion (B) of the pulmonary arch on the side opposite the definitive aortic arch persists (perhaps due to blood flow factors), there will be interference with the development described above, and the ventral portion (D) of this pulmonary arch may then be obliterated This will result in an "absent pulmonary artery" on this side, or rather in "proximal interruption of the pulmonary arch" (Figure 8e) The primitive pulmonary artery will remain intact, but will connect with the dorsal (B) portion (which will usually be subsequently recognized only as a fibrotic structure best identified as a ductus arteriosus, but which may persist as a patent vessel) rather than with the ventral portion (D) of the pulmonary arch (which would normally be incorporated into the definitive pulmonary artery) The absent pulmonary artery will always occur on the side opposite the larger ductal (dorsal) arch segment Since the normal heart usually has a left aortic arch and a left ductus arteriosus, the absent pulmonary artery will usually be on the right side In abnormal hearts with right aortic arches, the larger ductal segment would generally be expected to be on the right side (Figure 8b), and an absent pulmonary artery would then be on the left side (Figure 8f) In cases of absent left pulmonary artery with defects of the bulbis cordis, but with left aortic arches, one must assume that the dominant pulmonary arch was on the right Likewise, for those very rare cases of normal heart with left aortic arch and absent left pulmonary artery, one must assume that the dominant pulmonary arch was on the right The development of large bronchial vessels from the aorta to the affected lung in these cases can be viewed as a secondary process

Our theory appears to explain all cases It differs greatly from that of Emanuel and Pattinson[20] in that these workers implicated faulty absorption of the segment on the side of the ductus (dominant ductal side), whereas we implicate degeneration of the corresponding segment on the opposite side It differs from the interpretation of McKim and Wigglesworth[15] in that the latter workers did not refer to possible reversal of the dominant pulmonary arch in their cases of absent left pulmonary artery, and did not stress the asymmetrical development of the pulmonary arteries Since we ascribe great significance to the location of the dominant pulmonary arch (and its ductal segment), the next question which arises has to do with the factors determining arch dominance We have already assumed that the development features of the fourth arches will influence those of the sixth arches In addition, one can assume that faulty differentiation of the aortic sac and arterial trunk (common trunk) will

affect the location of the dominant pulmonary arch through its effect on the fourth arches, but may also be of more direct influence at times (as in tetralogy of Fallot with left aortic arch but with absent left pulmonary artery, and therefore a dominant right pulmonary arch by our theory) Actually, the bulbis cordis defects may well be a result of faulty aortic sac and arterial trunk differentiation, and the association of bulbis cordis defects with absent pulmonary artery probably is not one of cause and effect

The association noted between absent right pulmonary artery and abnormalities of the great vessels does not conflict with this theory, but is just as one might expect if arch differentiation is abnormal The infrequent occurrence of bilateral ductus arteriosus in cases of otherwise normal hearts and pulmonary arteries is certainly in line with our theory, yet its rare occurrence in no way negates it Moreover, it fits those cases of truncus arteriosus having absence of one pulmonary artery If the left pulmonary artery is absent in such cases, the right pulmonary artery arises from the right posterior aspect of the truncus, if the right pulmonary artery is absent, the left pulmonary artery arises from the left posterior aspect Collett and Edwards[23] list one case (Dickson and Fraser[24]) which would appear to be an exception, inasmuch as the right pulmonary artery was listed as arising from the left side of the truncus, however, examination of the original paper shows the description and drawing to be indeterminate and confusing on this point Another case (Shapiro[25]) of truncus is pertinent to the earlier discussion, this case had a left pulmonary artery arising from the left side of the trunk and a right innominate artery giving off a branch to the right lung, this latter vessel was not referred to as a ductus arteriosus, but it is certainly very suggestive of such a structure in view of the embryologic features already described

Diligent search for residual ductal structures in specimens of truncus arteriosus lacking both pulmonary arteries (given a separate classification by most workers) may demonstrate such structures This would of course immediately identify them as close relatives of cases with pulmonary arteries, since the presence of a ductus arteriosus indicates the earlier presence of a pulmonary arch It is much easier to accept faulty differentiation of the pulmonary arches, with subsequent degeneration of various structures, than to visualize complete failure of the sixth arches to form Failure of clear-cut dominance of one or the other pulmonary arch may result in two pulmonary arteries each with a functioning ductus arteriosus or in bilateral interruption of the proximal portions of the pulmonary arches Although this suggestion is included largely for speculation, the observation that unilateral absence of a pulmonary artery is apparently not due to an absence of a pulmonary arch should make one hesitant in invoking such an explanation for absence of both pulmonary arteries There may well be similar or closely related factors involved in the development of all defects of the aortic and pulmonary arches, truncus, and bulbis cordis

Since in all cases of absent pulmonary artery there appears to be

simply a break in pulmonary arch continuity, it would appear more appropriate to term this defect as "proximal interruption of the pulmonary arch" The primitive pulmonary arteries *per se* remain intact, whereas the proximal arch component of the definitive pulmonary artery is deficient Normally there is "distal interruption" of the pulmonary arch, so one must be careful to refer to these cases as "proximal interruption" Interruption of the pulmonary arches has much in common with interruption of the aortic arches, since in the latter too there is normal as well as abnormal interruption Likewise in each there may be failure of interruption, giving bilateral ductus arteriosus in the former and double aortic arch in the latter

The functioning of the ductus arteriosus before birth probably accounts for the failure of large bronchial arteries to develop on the involved side Also, it probably allows a near-normal development of the lung on the affected side [15] The decreased size of the lung on the affected side, as described in the majority of published cases, may well be due to differential postnatal growth resulting from differences in blood supply [15]

The autopsy findings in our cases followed exactly the pattern described by McKim and Wigglesworth,[15] and like two of their cases, involved bilateral ductus arteriosus Our case, like that of Emanuel and Pattinson[20], showed highly vascular adhesions between the affected lung and the chest wall (We assume that the branch from the left subclavian artery demonstrated by aortography supplied blood to this area)

Clinical and Physiological Features

If present as an isolated defect, congenital absence of one branch of the pulmonary artery has been usually described as essentially asymptomatic However, there may be a slight decrease in exercise tolerance and pneumonitis is said to be fairly common in the involved lung Hemoptysis occasionally occurs, and in at least one case ruptured of an arteriosclerotic bronchial vessel was established as the cause of death [13]

Absence of one of the pulmonary arteries can often be diagnosed on the ordinary chest roentgenogram[12, 17] The involved hemithorax is smaller and the heart and mediastinum are shifted to that side The involved lung is very radiolucent As mentioned earlier, angiocardiography provides an exact diagnosis Cardiac catheterization has been performed in only a few of the reported cases[9, 11, 13], and in these the resting pulmonary artery pressures were normal, with only a slight increase on exercise In the present case, aortography was useful in demonstrating the collateral blood supply to the affected chest, and in retrospect, indicated that the ductus arteriosus on each side was not patent

Studies of pulmonary function in published cases showed either normal or slight reduction in vital capacity, residual volume, and total lung volume[9, 11] Bronchospirometric studies using room air demonstrated normal ventilation in the involved lung but non-participation in oxygen uptake [9, 11, 18] It has been shown experimentally that as much as one third of the output of the left ventricle may go to the bronchial arteries of a lung in which the pulmonary artery has been ligated [26] Findlay and Maier[7]

suggested that the patient with a congenitally absent pulmonary artery may be benefited by the removal of the lung on the affected side, thereby decreasing the load on the left ventricle

The pulmonary pathology found in our patient was unusual The medial hypertrophy in the small arteries of the left lung was severe, the average cross-section area of the lumen being only about 12% of the total average cross-section area of the artery This degree of narrowing was probably sufficient to account for the high calculated total pulmonary resistance obtained at each cardiac catheterization The left lung of this patient accepted the total right ventricular output, and pulmonary flow in this lung could therefore be assumed to be twice normal These pulmonary changes differed somewhat from those seen in ventricular septal defect with "secondary" pulmonary hypertension In the latter there is usually intimal proliferation of the small pulmonary arteries in addition to some degree of medial hypertrophy when the resistances are in the range calculated for this patient The absence of intimal proliferation suggests a different pathogenesis between the pulmonary resistance in our case and the type seen in ventricular septal defect ("secondary") The thickness of the media compared to the total vessel size is greater in this patient's left lung than in normal newborns The total pulmonary resistance of 2585 dynes sec cm ^{5} obtained at the first cardiac catheterization is comparable to normal newborn resistances However, the finding of an increased resistance of 6200 dynes sec cm ^{5} at 13 months of age indicates that this is a progressive phenomenon and therefore represents more than a mere persistence of normal medial hypertrophy of the newborn

Even though the patient was over one year of age at the time of death, the finding of a closed foramen ovale suggests an interesting possibility If the foramen ovale closed prematurely, from days to weeks prior to birth, it would be expected that the left atrium and mitral valve would not be as large as normal because of diminished flow into this chamber through this normal fetal passage Thus, a relative mitral stenosis would be created This, however, might be minimal enough so that it would not be easily measured or observed by routine measures (in our specimen, the mitral valve was slightly smaller than normal, but was not stenotic) Similar pulmonary pathology has been noticed in mitral stenosis patients A combination of twice the normal pulmonary flow plus some degree of mitral obstruction might more readily account for the pulmonary pathology observed in this patient

Dammann and Ferencz[27] described the lung findings in McKim and Wiglesworth's case of "Eisenmenger complex" with absent left pulmonary artery[15] The small pulmonary vessels were thick walled in the right lung (lumen-wall ratio of 2 6) and thin walled in the left (ratio of 5 8) In this case, the right lung was said to be under the stress of a common ejectile force No physiological data were obtained, and therefore it is difficult to make comparisons with our case However, because of the presence of a ventricular septal defect in their patient, we assume that there may have been some degree of "secondary" pulmonary hypertension

Surgical Aspects

In our case, because of the presence and progression of pulmonary hypertension, it was considered inadvisable to remove the lung on the involved side In retrospect, inasmuch as this case appeared to have normal hilar and intrapulmonary vessels on the involved side, it would have been possible to do surgical correction or alleviation by making an anastomosis between the hilar portion of the right pulmonary artery and the main pulmonary artery by means of an arterial graft This same conclusion holds true both for cases of isolated absent pulmonary artery and for cases associated with tetralogy of Fallot In the latter instance it will be important to be prepared at the time of corrective surgery to bridge the interrupted portion of the artery with a graft Actually, one of our recent surgical cases was a four year old boy having a tetralogy of Fallot defect with left aortic arch and absent left pulmonary artery At surgery, the ventricular septal defect was closed and the infundibular pulmonary stenosis corrected The patient died and on routine autopsy no left pulmonary artery was identified In view of the findings of McKim and Wiglesworth[15], later examination was done, and this showed a blind pouch, 4 millimeters in diameter, corresponding to the hilar end of the pulmonary artery system, it gave rise to the normal system of pulmonary artery branches, and was connected proximally to a small occluded vessel which was undoubtedly a fibrosed ductus arteriosus

Whether the above contemplated surgery would have helped in our case, or whether it is ever indicated in the usual case of isolated absent pulmonary artery remains problematical It seems likely that the pulmonary stump or pouch at the hilus is about as large at birth as it will ever become, and thus surgery if it is to be done at all, perhaps should be done in infancy Maier[14] suggested that in one of his cases of absent right pulmonary artery with an anomalous vessel from the aorta supplying the lung, the proximal end of this anomalous vessel could have been transferred to the side of the main pulmonary artery From the autopsy findings, this case would seem to be different from the usual case of absent pulmonary artery, resembling the "ectopic" pulmonary artery of Frantzel's case already described

SUMMARY

Congenital absence of the right pulmonary artery is described in a male infant with pulmonary hypertension Gross and microscopic pathological findings are presented, as well as cardiac catheterization data and angiocardiographic findings A theory is presented which appears to explain all variations of absent pulmonary artery It is suggested that a more accurate term for this defect would be "proximal interruption of pulmonary arch" There is reason to believe that this condition is surgically correctable by means of an arterial graft

RESUMEN

La ausencia congénita de la arteria pulmonar izquierda se describe en el caso de un niño con hipertensión pulmonar Se presentan los hallazgos

macro y microscópicos así como los datos de angiocardiografía y cateterización cardiaca

Se muestra una teoría que parece explicar todas las variaciones de la arteria pulmonar ausente Se sugiere que se use un término más exacto para este defecto, el que sería "interrupcion proximal de un arco pulmonar" Esta es una razon para creer que este defecto puede corregirse por injerto arterial

RESUME

L'auteur decrit l'absence congénitale d'artère pulmonaire droite, chez un bébé du sexe masculin atteint d'hypertension pulmonaire Il présente les constatations anatomo-pathologiques macro- et microscopiques, ainsi que les résultats du cathétérisme cardiaque et les constatations angiocardiographiques L'auteur expose une théorie qui semble pouvoir expliquer l'absence d'artere pulmonaire quel qu'en soit le degre Il suggère qu'un terme plus precis soit adopté pour désigner cette altération, et qui pourrait être "interruption proximale d'un arc pulmonaire" Il y a des raisons de croire que cet etat peut être corrigé chirurgicalement au moyen d'une greffe artérielle

ZUSAMMENFASSUNG

Beschreibung eines angeborenen Fehlens der rechten Pulmonal-Arterie bei einem mannlichen Kind mit pulmonalem Hochdruck Makroskopische und mikroskopische pathologische Befunde werden vorgelegt, ebenso wie Herzkatheterwerte und angiografische Befunde Es wird eine Theorie entwickelt, die alle Variationen des Fehlens der Pulmonal-Arterie erklart Es wird angeregt, dass eine genauere Bezeichnung fur diesen Defekt gegeben ware mit "proxymaler Unterbrechung eines pulmonalen Bogens" Es ist Grund vorhanden anzunehmen, dass dieser Krankheitszustand chirurgisch mittels einer Arterienplastik behoben werden kann

REFERENCES

1 Fraentzel, O "Ein Fall von abnormer Communication der Aorta mit der Arteria pulmonalis," *Virchow Arch f pathol Anat u Physiol u f klin Med*, 43 420, 1868

2 Doring, H "Angeborener Defekt der rechten Lungarterie," *Studien z Path d Entwicklung*, 2 41, 1914 (quoted by Muller)

3 Muller, L "Über angeborene Atresie der rechten Pulmonalarterie bei ein Erwachsenen (Beitrag zur Kenntnis des Kollateralkreislaufs der Lunge)," *Ztschr f Kreislauffors ch*, 19 561, 1927

4 Ambrus, G "Congenital Absence of Right Pulmonary Artery with Bleeding into the Right Lung," *J Tech Methods*, 15 103, 1936

5 Miller, J F "Congenital Absence of Right Pulmonary Artery in Newborn Infant, with Resulting Necrosis of Lung and Spontaneous Pneumothorax," *Am J Dis Child*, 53 1268, 1937

6 Thomas, H W "Congenital Cardiac Malformations," *J Tech Methods*, 21 58, 1941

7 Findlay, C W, Jr and Maier, H C "Anomalies of Pulmonary Vessels and their Surgical Significance with Review of the Literature," *Surgery*, 29 604, 1951

8 Blalock, A "Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis," *Surg, Gynec and Obst*, 87 395, 1948

9 Madoff, I M, Gaensler, E A and Strieder, J W "Congenital Absence of Right Pulmonary Artery," *New England J Med*, 247 149, 1952

10 Nadas, A S, Rosenbaum, H D, Wittenborg, M H and Rudolph, A M "Tetralogy of Fallot with Unilateral Pulmonary Atresia A Clinically Diagnosable and Surgically Significant Variant," *Circulation*, 8 328, 1953

11 Steinberg, I, Dotter, C T and Lukas, D S "Congenital Absence of a Main Branch of the Pulmonary Artery," *J A M A*, 152 1216, 1953

12 Wyman, S M "Congenital Absence of a Pulmonary Artery Its Demonstration by Roentgenography," *Radiology*, 62 321, 1954

13 Flynn, J E, Siebans, A A and Williams, S F "Congenital Absence of a Main Branch of the Pulmonary Artery," *Am J Med Sc*, 228 673, 1954

14 Maier, H C "Absence or Hypoplasia of a Pulmonary Artery with Anomalous Systemic Arteries to the Lung," *J Thoracic Surg*, 28 145, 1954

15 McKim, J S and Wiglesworth, F W "Absence of the Left Pulmonary Artery A Report of Six Cases with Autopsy Findings in Three," *Am. Heart J*, 47 845, 1954

16 Alexander, S C, Fiegel, S J and Class, R N "Congenital Absence of the Left Pulmonary Artery," *Am Heart J*, 50 465, 1955

17 Abrams, H L and Kaplan, H S *Angiocardiographic Interpretation in Congenital Heart Disease* Springfield Charles C Thomas, 1956

18 Smart, J and Pattinson, J N "Congenital Absence of the Left Pulmonary Artery," *Brit Med J*, 4965 491, 1956

19 Moss, A J, Austin, W O and O'Loughlin, B J "Congenital Absence or Atresia of a Main Branch of the Pulmonary Artery," *Am J Dis Child*, 72 398, 1956

20 Emanuel, R W and Pattinson, J N "Absence of the Left Pulmonary Artery in Fallot's Tetralogy," *Brit Heart J*, 18 289, 1956

21 Bremer, J L "On the Origin of the Pulmonary Arteries in Mammals," *Anat Record*, 3 334, 1909

22 Congdon, E D "Transformation of the Aortic-Arch System During the Development of the Human Embryo," *Carnegie Contr Embryol*, 14 47, 1922

23 Collett, R W and Edwards, J E "Persistent Truncus Arteriosus A Classification According to Anatomic Types," *S Clinic N Am*, 29 1245, 1949

24 Dickson, W E C and Fraser, J "A Congenital Abnormality of the Heart and Blood Vessels," *J Anat and Physiol*, 48 210, 1914

25 Shapiro, P F "Detorsion Defects in Congenital Cardiac Anomalies," *Arch Path*, 9 54, 1930

26 Bloomer, W E, Harrison, W, Lindskog, G E and Liebow, A A "Respiratory Function and Blood Flow in Bronchial Artery After Ligation of Pulmonary Artery," *Am J Physiol*, 157 317, 1949

27 Dammann, J F, Jr, and Ferencz, C "The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease," *Am Heart J*, 52 210, 1956

Circulatory Changes Associated with Inspiratory Positive Pressure Treatment*

OSCAR FEINSILVER, M D , F C C P[**]
Worcester, Massachusetts

In the past decade there has been increasing application of positive pressure in the administration of oxygen therapy in the management of asthma and emphysema, as well as other conditions in which it was considered that this form of therapy might be of benefit The present study is limited to the application of positive pressure during the inspiratory phase of the respiratory cycle

Two types of apparatus were used, the Emerson Respiration Assistor,† and the Bennett Pressure Breathing Unit (Model TV-2P) These two appear to be similar in the amount of inspiratory effort required to evoke air flow under positive pressure, and in the readiness with which this flow is interrupted by the increased intrapulmonary resistance at the end of inspiration, permitting normal expiration to take place

A variety of opinions exists concerning the benefits of IPPB provided with this equipment Some of the leading proponents of this form of treatment have been Gordon,[1] Motley,[2] Trimble,[3] and Segal[4] Examination of the publications of Motley shows that changes in pulmonary function produced by treatment provided with Bennett equipment cannot be shown to be of statistical significance Segal[4] has shown that the use of IPPB, using Bennett equipment, without the aid of a bronchodilator actually brings about a reduction in vital capacity, timed vital capacity, and maximum breathing capacity However, when the use of a bronchodilator is combined with IPPB, the performance of these tests exceeds that observed following the use of a bronchodilator alone when the latter is provided with a hand nebulizer Other workers[5] have shown that no difference can be demonstrated between the benefits of an effective bronchodilator, nebulized with a pump or an oxygen tank, and the results obtained when IPPB is added to the routine

This study is not an attempt to mediate between the different points of view presented above It is concerned only with the circulatory changes associated with alterations in intrathoracic pressure which result from IPPB

Of fundamental importance to the behavior of the heart is its degree of filling in diastole This subject has been clearly presented by Wiggers[6] in his studies on Starling's law of the heart These studies show the fundamental dependence of the heart upon the blood reaching it through the great veins of the thoracic cavity Filling of the veins of the thorax, like the filling of veins everywhere, is a passive phenomenon, governed by the

*From the Medical Service, St Vincent Hospital
**Senior Visiting Physician, St Vincent Hospital
†Made available through the courtesy of J H Emerson Company, Cambridge, Massachusetts

pressures and forces surrounding them The forces associated with the respiratory effort are of great importance in this area During inspiration, as the intrathoracic pressure becomes lower than that within the abdominal cavity, the neck, and the upper extremities, blood is forced into the chest This process is promptly slowed during expiration as the intrathoracic pressure rises In individuals with severe asthma or emphysema, who must carry out something approaching the Valsalva maneuver with each expiratory effort, no blood can enter the chest during this phase of respiration It is to be expected that significant changes will take place when these individuals are subjected to IPPB Mixter[7] has shown that inspiration augments the return flow of blood of the inferior vena cava in anesthetized dogs Bjurstedt and co-workers[8] have shown marked lowering of the systemic blood pressure during exposure of anesthetized dogs to elevated intrapulmonary pressures of 40 cms of water for periods of 15 seconds Direct measurements in the superior vena cava were shown by Brecher and Mixter[9] to indicate increased venous return during inspiration, reduced by IPPB in the closed chest of anesthetized dogs It has been stated by Whittenberger[10] that, while venous return is initially decreased, there occurs a rise in peripheral venous pressure which reconstitutes the venous gradient thus re-establishing venous return It is considered by him, therefore, that venous return and cardiac output are only momentarily decreased because the reconstitution of a normal venous gradient maintains a normal cardiac output during positive pressure breathing It is warned, however, that individuals in shock or impending shock, who are not capable of achieving a compensatory rise in venous pressure, may indeed suffer a significant drop in cardiac output

Because of the increasing acceptance of this form of treatment, it was considered advisable to investigate further the influence of IPPB upon the circulation utilizing the dye dilution technique developed by Stewart[11] and

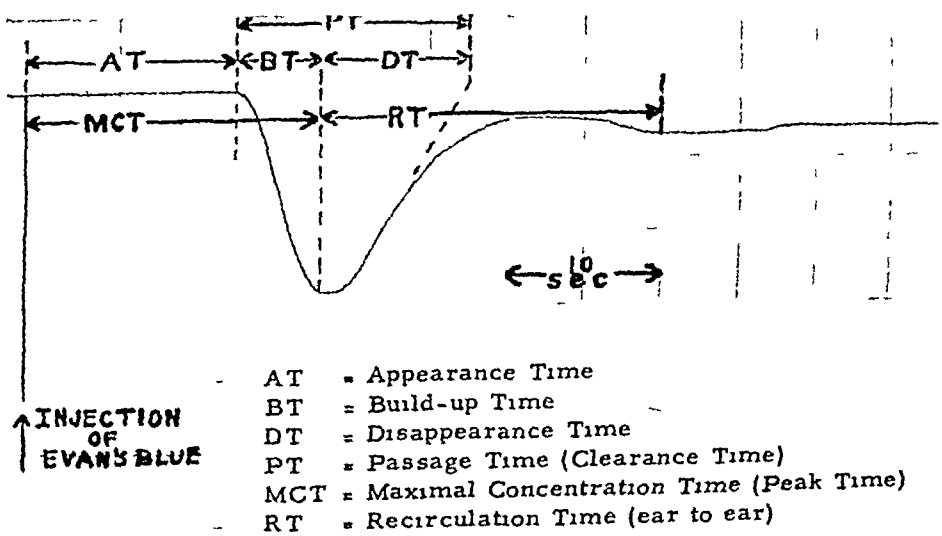


FIGURE 1 A dye dilution curve obtained by injecting 025 gm of Evans Blue dye into the superior vena cava The curve was registered with an ear oximeter and Leeds & Northrup recorder The nomenclature of the features of this curve is indicated

Hamilton,[12] and recently simplified by Wood and co-workers[13 14 15] using a recording oximeter This technique has been shown by these and other workers[16] to be useful in estimating with considerable accuracy the cardiac output and flow rates through any channel studied by suitable techniques

Technique Employed Nine patients were studied Three had unresolved pneumonia Two had asthma The remainder had pulmonary emphysema Of these, two had severe cor pulmonale All work was done with the patient in the semi-recumbent position in a quiet room at 7 00 A M before meals and other ward procedures could influence the circulatory status of the patient With a B L B mask 100 per cent oxygen was inhaled during the procedures in which a basal dye dilution curve was obtained and again during the administration of IPPB This precaution was considered advisable in order to eliminate the influence of any degree of anoxia and to guarantee a steady base line in the record Medication was eliminated from the apparatus during IPPB to avoid the possible influence on the circulation of the drugs commonly used However, moisture was continually provided The injection of dye was carried out as closely as possible at exactly five minutes from the time of onset of IPPB The equipment used was the single scale ear oximeter developed by Earl Wood This was used in conjunction with a Leeds & Northrup Speedomax, Type G, amplifier and recorder The latter was adjusted to a speed of 2 5 mm per second The oximeter ear piece was checked each time before use with filters of known transmission to insure correct operation The dye used was Evans Blue,* which has been found suitable because of the fact that the light absorbed by it was maximal at a wave length of 620-630 mμ, which lies in the red range of the photocell filter in the ear piece This photo-cell responds to changes in concentration of oxyhemoglobin which transmits light maximally in this range When oxygen saturation is kept constant, therefore, changes in transmission in this area represent changes in light absorbed by Evans Blue dye[13] Hence, transmission becomes a function of the concentration of Evans Blue A constant quantity of dye (025 gm), dissolved in 5 00 ml of water was used, injected with the identical number 18 needle and syringe, in order to avoid any variability from this source Injections were made as rapidly as possible, ordinarily accomplished in less than a second, into an antecubital vein A single pair of injections was carried out by way of a number 18 needle into a polyethylene catheter which had been previously introduced into the superior vena cava The dye in these injections was immediately flushed through the catheter with 5 00 ml of saline through a side adapter

Results Obtained The results obtained can best be interpreted using the terminology employed by Broadbent and Wood[16] as illustrated in Figure 1 Here is shown a dye dilution curve obtained when 025 gm of Evans Blue was injected into the superior vena cava through a polyethylene catheter The nomenclature adopted by Wood and his co-workers is provided

*Manufactured by the Waters Corporation, Rochester, Minnesota
Supplied through the courtesy of the Warner-Chilcott Laboratories, Morris Plains, New Jersey

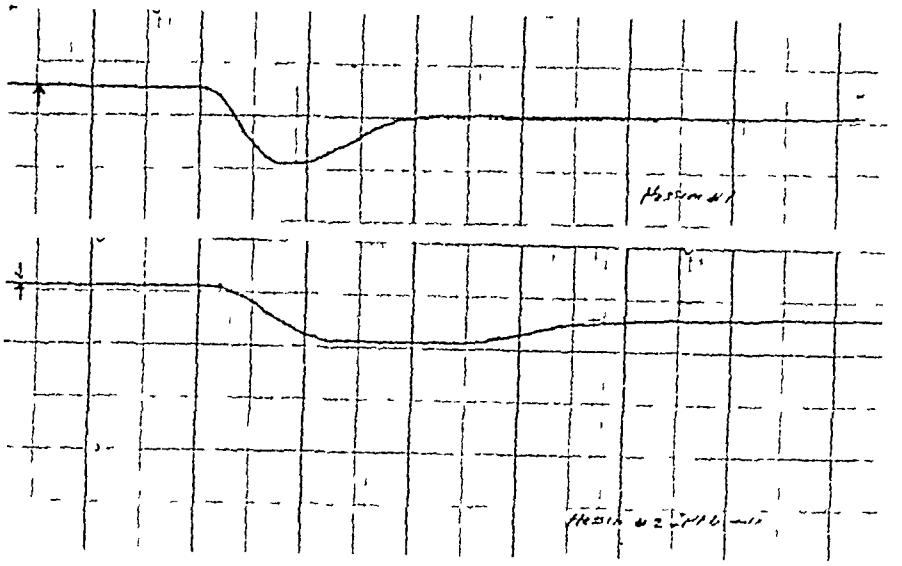


FIGURE 2 Upper tracing is a dye dilution curve obtained in a 55-year-old male while breathing 100 per cent oxygen Lower tracing was obtained breathing oxygen with IPPB at + 18 cms of water inspiratory positive pressure Flattening of the curve with marked prolongation of appearance time, build-up time, and disappearance time is noted A step-like return of the curve to the base line is noted Vertical lines represent one second intervals.

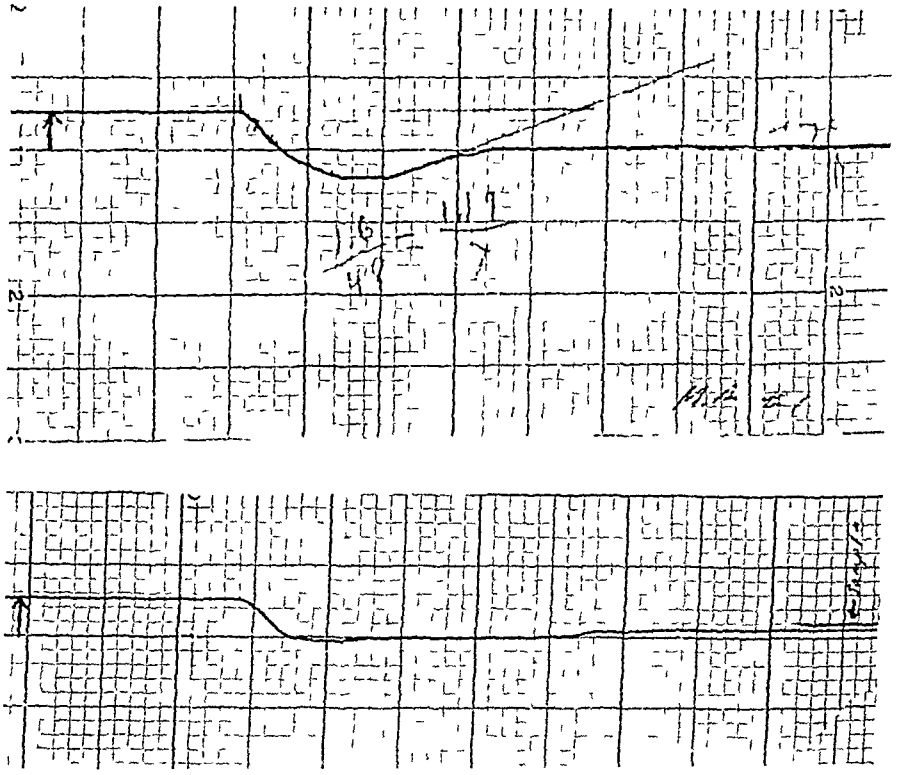


FIGURE 3 Upper tracing is a dye dilution curve in a woman of 35 breathing 100 per cent oxygen Lower curve was obtained while breathing oxygen at + 18 cms of water IPPB Prolongation of appearance time, disappearance time, and passage time are noted, with marked flattening of the curve Vertical lines represent one second intervals

It was noted that the contour of the curves obtained by the technique utilized differed somewhat from those obtained by injection of the dye into the superior vena cava The recirculation time was not detectable Furthermore, the contour underwent profound changes under the influence of IPPB No attempt was made, therefore, to utilize the curves for the estimation of cardiac output

Three examples of these changes are presented Figure 2 shows the changes undergone in a 55-year-old man with asthma who was given oxygen under a pressure of +18 cms of water during inspiration with Bennett equipment Flattening of the curve with marked prolongation of appearance time, build-up time, and disappearance time is noted A step-like return of the curve to the base line is noted Blood pressure dropped from 170/110 to 146/94 in 10 minutes

Figure 3 shows the changes undergone in a woman of 35 with unresolved pneumonia of the left lower lobe, given oxygen at +18 cms of water with Bennett equipment The changes noted are similar to those noted in Figure 2 Blood pressure dropped in ten minutes from 110/70 to 70/60

Figure 4 shows the changes in a 48-year-old man with unresolved pneumonia of the right upper lobe He was given oxygen at +18 cms of water with Emerson equipment The prolongation of appearance time, build-up time, and disappearance time is striking His initial pressure was 140/90 At six minutes, the patient indicated that he had a headache His blood pressure was recorded at that time as 90/80 At eight minutes, his pulse and blood pressure disappeared, and the experiment was quickly terminated

The detailed observations in all nine cases studied are listed in Table I

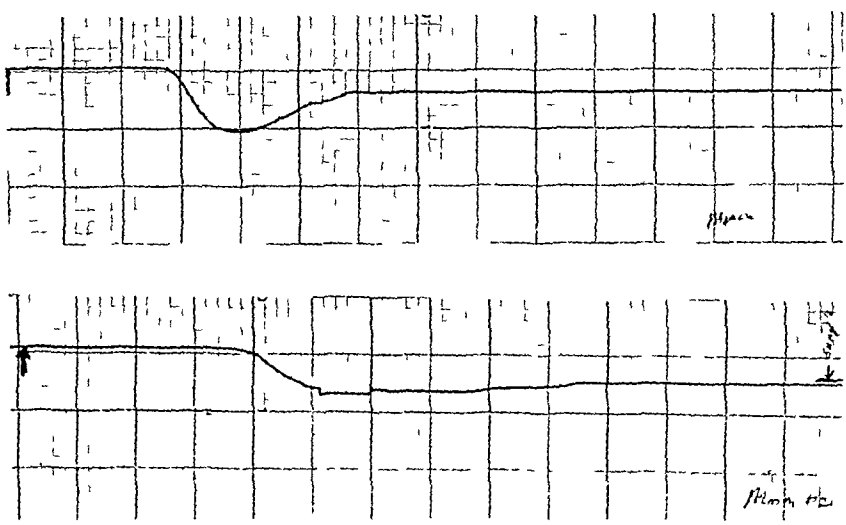


FIGURE 4 Upper tracing was obtained in a 48-year-old man breathing 100 per cent oxygen Lower curve was obtained while breathing oxygen at + 18 cms of water IPPB There is striking prolongation of appearance time, build-up time, and disappearance time An artifact due to jarring of the pen is noted at the peak of the build-up portion of the lower curve Treatment was terminated at eight minutes because of disappearance of pulse Vertical lines represent one second intervals

TABLE I

DETAILED OBSERVATIONS IN EACH OF NINE CASES STUDIED

	AT 10-20	BT 7-15	DT 9-26	PT 15-35	MCT 16-35	RT 16-28	B P Average
Cases							
P H (Asthma							
Basal Figures	15 5	7 5	19	26 5	23 0		170/110
IPPB Figures + 18 cms (Be)	17 5	11 0	34	45	28 5		146/94 at 10 min
T H (Cor pulmonale)							
Basal Figures	12 5	6 0	15 5	21 5	18 5		108/68
IPPB Figures + 18 (Em)	14 5	5 0	20 0	25 0	19 5		90/68 at 10 min
L M (Unresolved pneumonia)							
Basal Figures	13 5	5 5	12 0	17 5	19 0		140/90
IPPB Figures + 18 (Em)	19 0	8 0	41 0	49 0	27 0		0 at 8 min
J H (Asthma)							
Basal Figures	10 0	6 0	20 5	26 5	16 0		108/78
IPPB Figures + 10 (Be)	15 5	8 0	20 0	28 0	23 5		106/84 at 10 min
T H (Cor pulmonale)							
Basal Figures	21 5	10 0	27 0	37 0	31 5		108/68
IPPB Figures + 10 (Em)	27 0	8 5	42 0	50 5	35 5		90/68 at 10 min
J C (Emphysema)							
Basal Figures	13 5	11 0	17 0	28 0	24 5		110/60
IPPB Figures + 5 (Em)	18 5	13 0	33 0	46 0	31 5		92/80 at 10 min
M A (Unresolved pneumonia)							
Basal Figures	12 5	7 0	15 0	22 0	29 5		110/70
IPPB Figures + 18 (Be)	15 0	6 0	60 0	66 0	31 0		70/60 at 10 min
N G (Emphysema)							
Basal Figures	14 0	5 0	13 0	18 0	19 0		104/70
IPPB Figures + 18 (Em)	16 5	5 5	16 0	21 5	22 0		90/60 at 10 min
C T (Unresolved pneumonia)							
Basal Figures	13 5	5 0	10 5	16 0	19 0		100/68
IPPB Figures + 18 (Em)	18 0	8 5	16 5	25 0	26 5		94/66 at 10 min

Figures indicate seconds

AT—Appearance Time
BT—Build-up Time
DT—Disappearance Time
Be—Bennett equipment
RT—Recirculation Time
MCT—Maximum Concentration Time
RT—Recirculation Time
Em—Emerson equipment

These results are further analyzed in Table II

TABLE II
ANALYSIS OF OBSERVED DATA

Total Cases—9		Unresolved pneumonia 3 Asthma 2 Emphysema 2 Cor pulmonale 2
	Pressures applied during inspiration +5 to +18 cms water	
Appearance Time	Uniform prolongation 2 to 5 5 seconds, average 4 0	
Build-up Time	6 showed increase from 5 to 3 5 seconds, average 2 3 3 showed decrease from 5 to 1 5 seconds	
Disappearance Time	8 showed increase from 3 to 45 seconds, average 17 1 One showed decrease to 5 seconds	
Passage Time	All showed increase from 1 5 to 44 0 seconds, average 15 8	
Maximum Concentration Time	All showed increase from 1 0 to 8 0 seconds, average 5 0	
Blood Pressure	Changes in systolic level from 2 to 34 mm Changes in diastolic level variable Changes in pulse pressure uniformly lowered One patient in shock at 8 minutes	

SUMMARY AND CONCLUSIONS

A study of circulatory changes associated with Inspiratory Positive Pressure Breathing (IPPB), has been carried out in nine patients Inspiratory positive pressure varying from +5 to +18 cms of water was provided with Emerson and Bennett equipment In every case, there was a drop in pulse pressure due to lowering of the systolic level and variable changes in the diastolic level In one case, the blood pressure and pulse disappeared at eight minutes Dye dilution curves were obtained as closely as possible at five minutes from the onset of IPPB These showed marked alterations in all recognizable features when compared with previous curves obtained while inhaling 100 per cent oxygen There was uniform delay in appearance time, passage time, and in maximum concentration time in every case, with prolongation of build-up time and disappearance time in most cases studied The portion of the curve returning to the base line showed, almost invariably, a step-like appearance suggesting intermittent dilution of the bolus of dye by successive streams of blood entering the circulation in place of the smooth return ordinarily noted The total picture adds up to a profound disturbance in intrathoracic circulation resulting from this treatment

Under the circumstances, it is felt that this form of treatment should be provided only when indications for its use are clear-cut, and when used, continuous close observation of the patient is essential

RESUMEN Y CONCLUSIONES

Se ha hecho un estudio de los cambios circulatorios que se asocian al uso de los aparatos de presión inspiratoria positiva (IPPB) en nueve enfermos Las presiones positivas inspiratorias que varían de +5 a +18 cms de agua ce aplicaron con los aparatos de Emerson y Bennett

En todos los casos hubo una caída de la presion arterial debida al descenso del nivel sistólico y cambios variables en el nivel diastólico En un caso la presion arterial y el pulso desaparecieron a los ocho minutos Las curvas de dilución de colorante se obtuvieron tan exactamente como posible a los cinco minutos de empezarse a usar el IPPB Estas curvas mostraron marcadas alteraciones en las caracteristicas reconocibles cuando se compararon con las curvas previas obtenidas durante la inhalación de oxígeno a 100 por ciento Hubo retardo uniforme en el tiempo de la aparición, tiempo de paso, y tiempo de concentración máxima en todos los casos con prolongación del tiempo de levantamiente y de desaparición en la mayoría de los casos estudiados

La parte de la curva al volver a la línea basal mostró casi invariablemente una apariencia de escalones sugiriendo una dilución intermitente del bolo de colorante por corrientes sucesivas de sangre que entraban en la circulación en lugar del retorno uniforme ordinariamente observado

El cuadro en conjunto se agrega al trastorno profundo de la circulación intratorácica que resulta de este tratamiento

Bajo estas circunstancias se cree que esta forma de tratamiento debe darse sólo cuando las indicaciones para su uso sean precisas, y cuando se use hay que observar al enfermo muy cuidadosamente

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

Es wurde an 9 Patienten eine Untersuchung der Kreislaufveranderungen vorgenommen, die mit der inspiratorischen positiven Druckatmung (IPPB) verknupft sind Der inspiratorische positive Druck, variierend von +5 bis +18cm Wasser wurde mit der Ausrustung nach Emerson und Bennett erzeugt In jedem Fall bestand ein Abfall des Pulsdruckes infolge Verringerung des systolischen Druckwertes und schwankenden Veranderungen des diastolischen Wertes In einem Fall verschwanden Blutdruck und Puls nach 8 Minuten Farbstofflosungskurven wurden sobald wie moglich gewonnen 5 Minuten nach dem Beginn der IPPB Diese zeigten ausgepragte Veranderungen in allen erkennbaren Merkmalen im Vergleich mit vorausgegangenen Kurven, die unter Inhalation von 100%-Sauerstoff gewonnen wurden Es bestand einheitlich eine Verzogerung in Zeitpunkt des Auftretens, der Passagezeit und der Zeit der maximalen Konzentration in jenem Fall mit Verlangerung der Aufbauzeit und Verringerung der Auflosungszeit in den meisten der untersuchten Falle Der sich zur Ausgangslinie zuruckwendende Abschnitt der Kurve zeigte fast unveranderlich ein schrittweises Auftreten, das die Vermutung einer intermittierenden Losung der Farbstoffpartikel erweckte infolge succesiven Eintretens des Blutstromes in den Kreislauf anstelle der gleitenden gewohnlich beobachteten Ruckkehr Der Gesamteindruck rundet sich ab zu einer eingreifenden Storung der intrathorakalen Zirkulation als Folge dieser Behandlung

Unter diesen Umstanden hat man das Empfinden, als sollte diese Art der Behandlung nur angewnadt werden, wenn klare Indikation fur ihren Ein-satz bestehen Wird sie angewandt, ist fortlaufende Beobachtung des Kranken wesentlich

REFERENCES

1 Gordon, B, Motley, H L, Theodos, P A, Lang, L P and Tomashefski, J "Considerations of the Clinical and Physiologic Factors in the Treatment of Chronic Pulmonary Conditions," *Dis Chest*, 19 271, 1951

2 Motley, H L and Tomashefski, J F "Treatment of Chronic Pulmonary Disease with Intermittent Positive Pressure Breathing," *AMA Arch Indust Hyg and Occup Med*, 5 1-8, 1952

3 Trimble, H C and Kiernan, J "Pulmonary Emphysema Treated by Intermittent Positive Pressure Breathing," *J Amer Ger Soc*, 2 102, 1954

4 Segal, M S, Solomon, A, Dulfano, M J and Herschfus, J A "Intermittent Positive Pressure Breathing," *N E J Med*, 250 225, 1954

5 Miller, R D, Fowler, W S and Helmholtz, H F, Jr "Treatment of Pulmonary Emphysema and of Diffuse Pulmonary Fibrosis with Nebulized Bronchodilators and Intermittent Positive Pressure Breathing," *Dis Chest*, 28 309, 1955

6 Wiggers, Carl J "Circulatory Dynamics," *Grune & Stratton, New York*, 1952

7 Mixter, G, Jr "Respiratory Augmentation of Inferior Vena Flow Demonstrated by a Low-Resistance Phasic Flowmeter," *Am J Physiol*, 172 446, 1953

8 Bjurstedt, H, Wood, Earl H and Astrom, A "Cardiovascular Effects of Raised Airway Pressure," *Acta Physiol Scand*, 29 190, 1953

9 Brecher, G A and Mixter, G "Effect of Respiratory Movements on Superior Cava Flow Under Normal and Abnormal Conditions," *Am J Physiol*, 172 457, 1953

10 Whittenberger, J L and Sarnoff, S J "Physiologic Principles in the Treatment of Respiratory Failure," *Med Clin North Amer*, 34 1335, 1950

11 Stewart, G N "The Output of the Heart in Dogs," *Am J Physiol*, 57 27, 1921

12 Hamilton, W F, Moore, John W, Kinsman, J M and Spurling, R G "Simultaneous Determination of the Pulmonary and Systemic Circulation Time in Man and a Figure Related to the Cardiac Output," *Am J Physiol*, 84 338, 1928

13 Nicholson, John W III and Wood, Earl H "Estimation of Cardiac Output and Evans Blue Space in Man, Using an Oximeter," *J Lab and Clin Med* 38 588, 1951

14 Beard, E F and Wood, E H "Estimation of Cardiac Output by the Dye Dilution Method with an Ear Oximeter," *J Applied Physiol*, 4 177, 1951

15 Warner, H R and Wood, E H "Simplified Calculation of Cardiac Output with an Ear Oximeter," *J Applied Physiol*, 4 177, 1951

16 Dow, Philip "Estimation of Cardiac Output and Central Dilution Blood Volume by Dye Dilution," *Physiol Rev*, 36 77, 1956

17 Broadbent, James C and Wood, Earl H "Indicator-Dilution Curves in Acyanotic Congenital Heart Disease," *Circ*, 9 890, 1954

The Treatment of Chronic Coronary Heart Disease

The terms angina pectoris, coronary heart disease, heart pain, and coronary insufficiency will be used synonymously and interchangeably throughout this article We shall define angina pectoris as that distress which occurs whenever there is a disproportion between the oxygen need of the myocardium and the oxygen being supplied to the myocardium at that particular moment It becomes obvious that there are many conditions which may produce angina pectoris, for example

1 Actual disease of the coronary arteries, such as arteriosclerosis, etc
2 An inability of the blood to carry oxygen to the heart muscle such as occurs in chronic anemias, pernicious anemia, chronic carbon monoxide poisoning, etc
3 A failure of the filling of the coronary arteries as may occur in severe aortic and/or mitral stenosis
4 A physiological interference of the filling of the coronary arteries as is seen in the paroxysmal arrhythmias, etc
5 Alterations in the mean aortic blood pressure as is found in aortic insufficiency
6 A disproportion between the blood vessel supply and the muscle bulk of the ventricle as is seen in severe myocardial hypertrophy
7 Lastly there are many instances in which no definitive cause can be found to explain the patient's pain

The diagnosis is made by history alone The patient states that as a result of physical effort or emotional excitement he sustains some type of pain somewhere in his body which is relieved by rest and/or by nitroglycerin There is no laboratory test or physical finding that is pathognomonic of angina pectoris

The patient suffering from this disease must have a complete history as well as a thorough physical examination, complemented and supplemented by all indicated laboratory procedures In addition we would suggest that routine gall bladder and complete gastro-intestinal x-ray examinations be done as well as studies of thyroid function

Treatment of Angina Pectoris

This discussion will be limited to our personal treatment in coronary heart disease The treatment of angina pectoris must be, first of all, the treatment of all concomitant diseases that may be present They may be treated simultaneously with the treatment that is directed to relieve the coronary pain Often the correction of an anemic condition, relief of a hyperthyroid state etc , can greatly reduce the number of anginal seizures

Our Treatment for Chronic Coronary Heart Disease Depends Upon Education

By education we mean the explanation to the patient and to his closest relative the nature of coronary disease We relate all pertinent information both to the individual and his closest relative It has been our experience that the patient and his family appreciate understanding the nature of this disease The patient must be reassured that the diagnosis does not connote either sudden or impending death He must be constantly reassured that people with this disease can and are able to live a normal or nearly normal life It is emphasized that any restriction in his activity is the result of the disease itself The activity or limitation of activity placed upon the patient should be judged entirely by the patient's symptoms We ourselves place no limitation upon the patient The physician and the patient seek through trial and error to find those adverse things that may produce pain We discuss with the patient any restrictions that are necessitated by this trial and error method, and select the course best suited for the individual to carry on his life We teach the patient to live within his pain or cardiac reserve

Drugs

Anticoagulants We do not use anticoagulants routinely We restrict their use to those individuals who have had repeated myocardial infarctions, frequently recurring anginal attacks, previous embolic phenomena, or who have some extra cardiac condition indicating their need We use dicumarol in individual daily doses in a strength that will maintain a prothrombin activity of between 20 and 30 per cent of normal This must be determined empirically

Atropine Sulfate Atropine sulfate is used in doses of gr 1/200 or 1/150 It is frequently used for post-prandial anginal distress Our favorite prescription is

Calcium Carbonate	gr	V
Magnesium Oxide	gr	V
Bismuth Subnitrate	gr	V
Atropine Sulfate	gr	1/150
Sodium Phenobarbital	gr	ss
Soda Bicarbonate q s	gr	xxx

Directions The patient takes one powder tid pc and also at bed time if needed

Digitalis Digitalis is indicated in the presence of heart failure We still use the whole leaf form and restrict the glycoside for rapid digitalization We have selected digitora as the product of our choice The grains 1 28 tablet is for practical purposes one cat unit The patient is digitalized by giving one cat unit for every 10 pounds of body weight in divided doses over a period of about one week Once digitalization is completed the effect of the digitalis is maintained by a maintenance dose This usually is one cat unit daily Digitoxin is used orally for rapid digitalization with a total of 1 2 mg being the average digitalization dose The maintenance

dose varies from 1 to 2 mg daily. If the patient is vomiting we use Cedilanid intravenously, 8 cc of the drug being the usual digitalizing dose and the maintenance dose varying from two to four cc daily

Diuretics The prophylactic use of a diuretic in conjunction with digitalization will often relieve the patient of "Nocturnal Angina" We use Salyrgen Theophylin in a dosage of 1 cc intramuscularly as often as is needed to yield the desired therapeutic effect

Iatrogenic Hypothyroidism The creation of various degrees of hypothyroidism has been suggested for the treatment of severe coronary or intractable angina pectoris We seldom use this form of therapy It is our belief that there are very few individuals suffering from "intractable angina" We feel that in all likelihood we are dealing with an "intractable patient" with angina rather than an "intractable angina" The hypothyroidism may be instituted by surgical removal of the thyroid gland, by the use of anti-thyroid drugs such as propylthiouracil or fractionated doses of radio-active iodine Surgery and x-ray irradiation are seldom used At the moment radioactive iodine is most popular

Nitroglycerin We depend on nitroglycerin for the treatment of angina pectoris The patient is taught to use the drug therapeutically and prophylactically The average doses varies from gr 1/200 to gr 1/100 The patient places the tablet under his tongue and as soon as it is dissolved there is relief of pain We suggest that the patient should use the tablet at the onset of his pain and not wait until the pain is fully developed If the patient must perform some act which he knows from previous experience will produce pain we suggest he take the nitroglycerin tablet before he performs the act We rarely use any other treatment for the acute attack

Quanidine Sulfate This drug is used both therapeutically and prophylactically to control the arrhythmias The dose is gr 3 four times daily or every four hours "around the clock" The individual dose is increased gradually until the desired therapeutic effect is obtained, then the effect is maintained by a maintenance dose

Sedatives These are used when indicated and we have a preference for mebarol gr 3/4 q i d Patients are usually not familiar with this drug and do not confuse it with phenobarbital

Surgery A surgical procedure that is indicated can be performed safely in patients with coronary heart disease Many times the removal of a diseased gallbladder etc, will diminish the number of anginal attacks We know of no contraindication to surgery in the patient with chronic coronary disease It is essential, however, that one have the anesthesia administered by a trained anesthesiologist

Surgical procedures relative to the relief of coronary artery pain or as an attempt to revascularize the heart are many We do not recommend any surgical procedure for the treatment of angina pectoris It is our belief that any results obtained are psychological and not physiological

Tranquilizers The tranquilizers are used only if indicated May we suggest that the patient should be constantly observed for the side effects

that can occur from the use of these drugs and particularly bizarre and unusual psychotic reactions

Usurp

To usurp means to "use without authority" Too often physicians without proper reason will elect to restrict and regulate the life of patients This self-appointed dictatorial approach in the treatment of angina pectoris is totally unwarranted

Coitus

If the patient has no pain or anginal distress during or after coitus no restrictions or suggestions are needed Occasionally a patient may develop impotence either because of the fear of the act or because he has experienced anginal pain during the act In these instances reassurance and reeducation is necessary In this event we suggest the pre-coital use of nitroglycerin which will often abolish the seizure We also suggest that the normal partner take over the active role in the coital act We advise the patient and his partner to discuss the problem with us should further difficulties arise

Alcohol

We do not recommend or advise the use of alcohol in any form in the treatment of angina pectoris It has no physiological effect on the coronary circulation and too often the patient develops a therapeutic enthusiasm that necessitates the change of treatment from angina to that of alcoholism May we suggest at this time that we do not alter the patient's smoking habits unless smoking produces chest pain

Tension

The individual is taught to avoid all forms of nervous tension and emotional fatigue He is instructed particularly in avoiding emotional upsets, strain, worry or anger The drugs outlined above may be used to assist the patient during this particular phase of his treatment We frequently advise the reading of "How to Live 365 Days a Year" by Dr Schindler The patient may be referred to Group Therapy, if it is available in the community We must spend time with the patient and his associates in overcoming the anxiety and fear he has concerning his disease, the anxiety and concern he has in regard to returning to normal activity, and, particularly, in overcoming the reactive depression in his illness

Iatrogenic

The physician must be careful both in his actions and speech to avoid creating disability and fear in the victim of coronary heart disease It is possible for the physician to transfer to the patient his own emotional immaturity and/or his lack of knowledge concerning the method of handling the victim of coronary heart disease Should the physician find it difficult to handle the emotional factors in the patient's illness it would be better for the physician and the patient if the patient be referred to a physician so disciplined

Optimism

Optimism is the watchword in the treatment of these patients There is no room for pessimism and no room for unneeded and unwarranted re-

strictions in their life It is the duty of the attending physician to constantly "preach the gospel of optimism" He must reinforce this optimism by indoctrinating this philosophy in the patient, his family and associates He must return the patient to his job and to his place in society as quickly as possible The *only restrictions* to be placed on the individual are those that arise in the limits of the area of his pain reserve or his cardiac reserve He can do anything he wants to do as long as it does not produce distress He may ride in planes as long as they are pressurized but he must not pilot a plane Should he experience pain in anticipation of his flight or repeated pain during flight he should avoid air travel He may drive his car if driving does not exasperate him If, however, he experiences pain while he is driving he should pull to the side of the road and remain there until the attack of pain stops The patient is taught moderation but not restriction The patient is advised not to become over fatigued and not to do anything to excess Rest periods are often of value to these people He should avoid undue physical exertion particularly during inclement weather The "optimism treatment" must be constant and in full doses

Nutrition

Diet If the patient has good eating habits and there is no indication for a special diet he receives no dietary instructions If he has an allied disease that requires dietary management the indicated diet is furnished If the patient is obese he receives a 1200 calorie diet which is supplemented by a daily multiple vitamin mixture He remains on this routine until his weight is normal Low sodium diets are administered when indicated The low fat or low-cholesterol diets are not prescribed unless they are indicated If desired, one may also prescribe the proprietary preparations that assist in lowering blood cholesterol levels The patient is taught to avoid overeating and overdrinking, to eat slowly and to chew his food well Flatulence is relieved by the use of the powder above outlined and constipation is treated when present The patient is taught not to strain at stool

Summary

Our treatment of angina pectoris depends on

1 Accurate diagnosis
2 The treatment of allied and concomitant diseases
3 EDUCATION of the patient, his family and his associates

CONCLUSION

We place no arbitrary restrictions on the victim of coronary heart disease The only restrictions are those within his own pain or cardiac area He is taught to live a normal life or as nearly normal life as it is possible for him to live In our efforts to Add Years To His Life we must remember that in doing so we must be certain we are Adding Life To Those Years

JOHN FRANCIS BRIGGS, M D, F C C P*
and JAMES BELLOMO, M D
St Paul, Minnesota

Associate Professor of Clinical Medicine, University of Minnesota

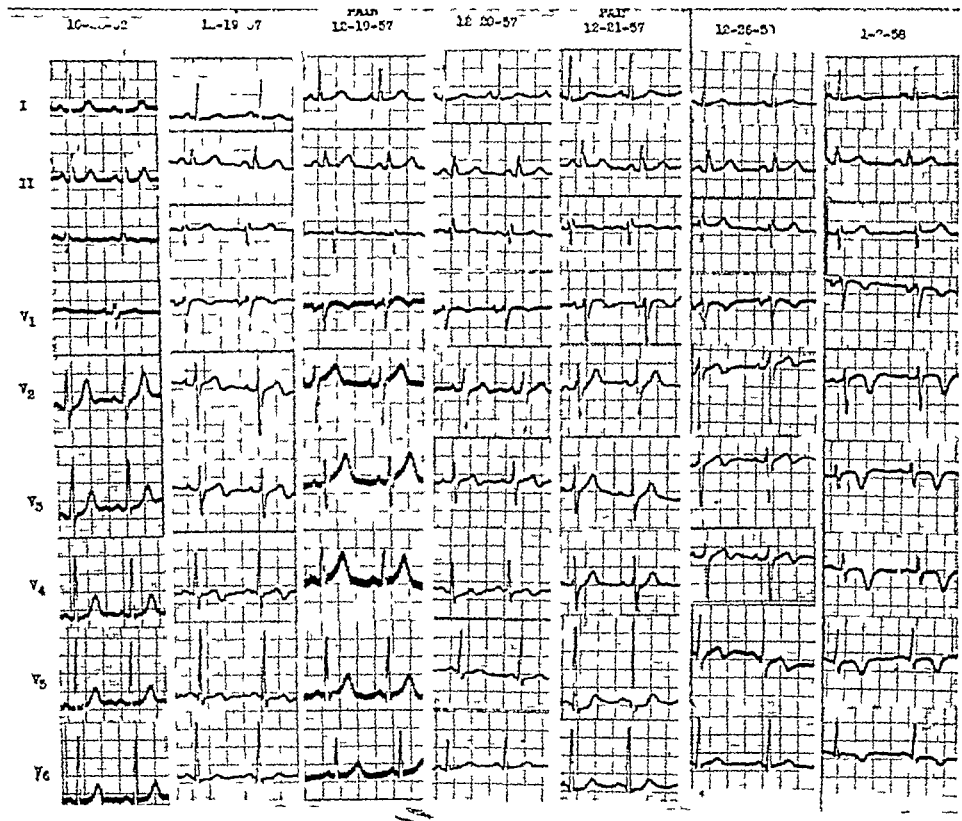
THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanation offered

---

A 59 year old man developed paroxysms of pain beginning in the right arm, and spreading to the right shoulder and the right lower jaw During three of these attacks electrocardiograms were recorded that were entirely normal and identical to the tracing (October 22, 1952) made five years before the attacks began No electrocardiograms had since been made in the absence of pain Accordingly when he was first seen by one of us (M G) an interim tracing (December 19, 1957) was made Later on the same day a paroxysm of pain occurred during which another electrocardiogram (December 19, 1957 pain) was recorded On the following day another interim record was made On December 21, 1957 another attack of pain occurred

In this case the electrocardiograms were normal during attacks of pain, and abnormal in the interim Viewed superficially this is the opposite of what occurs in most cases of angina pectoris so that this phenomenon has been dubbed "paradoxical" Actually it is not paradoxical at all The explanation is rather simple Several attacks of angina had left a degree of "ischemia" presumably in the epicardial layers of the anterior wall of the left ventricle, as evidenced by the terminal inversion of the T waves in the precordial leads of the interim tracings During an attack of angina, if and when the classical injury effects occur in the epicardial layers of the anterior wall of the left ventricle, the RS-T segments (and usually also the T waves) of the precordial leads are displaced upward In this case, as they not infrequently do, they reverse the direction of the previously inverted T waves (of the precordial leads) In short, as in any case, the electrical effects of the current of injury are in a direction opposite to that of the electrical effects of ischemia in the same zone In most cases of angina the affected zone seems to be endocardial



101
COLLEGE

Under this circumstance the current of injury results in *downward* shifts of the RS-T segments in the precordial leads and if a degree of ischemia is left after the attack the T waves are *increased* in height (in contradistinction to the effect of epicardial involvement) Since even large increases in the height of the T waves of the precordial leads cannot often be recognized as abnormal, the electrocardiogram is "normal" between attacks and shows abnormality (RS-T shifts) only during the attacks Thus the so called "paradoxical" events shown in Figure 1 are simply determined by the fact that the affected area is in the epicardial zone rather than in the more usual endocardial zone The smaller R waves in the anterior and left precordial leads in the last record suggest that some infarction has occurred but this was not confirmed by other laboratory findings Variation in placement of the electrodes may account for this change

The important practical point that is emphasized by this case is the following

In the investigation of pain in the chest it is important to record electrocardiograms *during the attack*, but it is also important to record the electrocardiogram *between* attacks Actually, having succeeded in gaining an opportunity to make tracings during or shortly after an attack of pain, *whatever* the appearance of that tracing, one should administer nitroglycerin and continue to make records at short intervals until the tracing ceases to change It is the series of changes that is diagnostic

MANUEL GARDBERG, M D and IRVING L ROSEN, M D *
New Orleans, Louisiana

*From the Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School

The Surgical Treatment of Tetralogy of Fallot*

Report of the Section on Cardiovascular Surgery
American College of Chest Physicians**

Since the introduction of the Blalock-Taussig systemic pulmonary anastomosis in 1945, the Potts-Smith aorticopulmonary anastomosis in 1946 and the Brock direct pulmonary valvulotomy in 1948, a significantly large group of patients suffering from the tetralogy of Fallot has been treated by these surgical methods This experience has demonstrated clearly that in the majority of these individuals a great deal of benefit has been derived and that the postoperative mortality rates, early and late, have been reasonably low A comparison of the results obtained by the three methods indicates that the overall results are not strikingly different "Good" or "very good" results have been reported in roughly 75 per cent of cases, with mortality rates approximating 10 to 15 per cent

Until recently, such beneficial results left little, if any, question regarding the advisability of recommending one of these operations even though the ideal of any surgical procedure, that is, complete correction of all of the defects present, admittedly was unattainable However, recent progress in the development of the various cardiac by-pass techniques, which in most instances makes possible the ideal of complete correction of the defects, calls for reappraisal of the surgical indications

In an attempt to establish the indications for the various procedures in view of our present knowledge, the Section on Cardiovascular Surgery of The Committee on Cardiovascular Disease of the American College of Chest Physicians sent questionnaires to the various members of its Advisory Committee throughout the world Thirty-nine of the Committee members responded giving information based on their experience with a total of 4062 cases Unfortunately, the questionnaires were answered in such a manner that in discussing many specific phases of the problem only a part of the total number of cases could be included Still, many significant facts have been obtained which should be of definite help to us as physicians in properly advising the patients who come under our care

Analysis of Results

1 *Operative Mortality Rates*

A comparison of the results obtained in a total of 2439 cases is given in Table I

The total mortality rates for the different procedures were quite similar with the exception that resection of an infundibular obstruction when associated with the various open techniques was over twice that of the indirect methods However, the results obtained with the open techniques must be given further consideration As shown in Table II, the number

---

Presented at the 24th Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

* Compiled and prepared by W R Rumel, M D , F C C P , Salt Lake City, Utah

TABLE I

OPERATIVE MORTALITY RATES (2439 CASES)

Number of Cases	Procedure	Deaths (Per Cent)		
		To 3 Months	Over 3 Months	Total
1497	Subclav-Pul Anast	13 8	5 3	19 1
515	Aortic-Pul Anast	10 6	6 6	17 2
238	Pul Valvulotomy	16 3	2 9	19 2
67	Infundibulectomy (Closed)	23 8	2 9	26 7
122	Open Repair	38 5	0 8	39 3

of cases reported by the various surgeons was of significant size in only two instances, being 54 and 48 respectively

These two surgical groups reported over 80 per cent of the total of the 122 open procedures The total mortality rate in the two averaged 28 4 per cent, which is definitely higher than that associated with the simpler techniques allowing for incomplete correction but which is not prohibitive in the developmental stages of a technique making possible complete correction of all of the defects present A cardiac by-pass method was employed in 110 of the 122 open operations One case was done under hypothermia and in the remaining 11 the technique was not specified As is generally true in the development of any new technique, a significant decrease in the operative mortality rate has been reported by one

TABLE II

MORTALITY RATES
OPEN REPAIR-TECHNIQUE UNSPECIFIED (112 CASES)

Number of Cases in Group	Per Cent		
	To 3 Months	Over 3 Months	Total
54	25 9	1 8	27 7
48	29 1		29 1
2	50 0		50 0
5	100 0		100 0
4	100 0		100 0
3	100 0		100 0
2	100 0		100 0
1	100 0		100 0
1	100 0		100 0
1	100 0		100 0
1	100 0		100 0

group as experience with the method has increased In 1955, the operative mortality rate in nine cases was 55 per cent, in 1956 in 28 cases, 28 5 per cent and up until May 1957, in 11 cases the rate was only 9 per cent Although no conclusions can be drawn on such a short term follow-up, still the trend seems encouraging In the remaining 20 cases, representing the early experience of nine different surgical teams from different areas, the mortality rate was 95 per cent, there being only one survivor This points out vividly that the development and application of one of these technical methods should not be undertaken lightly by an individual or group of individuals, since obviously the risk to the patient in the early experience is exceedingly high It also brings up another problem which is difficult or impossible to answer on the basis of statistics, but which most certainly should be given conscientious consideration before anyone embarks upon the task of developing one of these techniques The question is From a *practical standpoint,* how many such surgical units are really necessary in a given geographic area to handle adequately and safely the patients from this area who will require this type of highly specialized care? If a hypothetical geographical area had a maximum potential of 20 cases annually, then this area most certainly would not need three units and perhaps the interests of *all concerned* would be served better if no unit at all were set up, assuming, of course, that other workable arrangements could be made to provide the patients with the care they need Other obvious ramifications of this question, which must be settled after adequate deliberation seasoned with practicality, concern physician and hospital competition and the moral responsibilities to patients of those providing medical care This, in turn, brings up the question as to how many more cardiovascular surgeons are needed in our nation to best serve the interests of both the doctor and the patient An answer is suggested by the surprisingly small total number of cases of the various surgical procedures reported by the members of the surgical advisory committee who are prominent surgeons in their respective geographical areas (Table III)

Since these cases have been done over a period of approximately 10 years one must be led to believe that the potential reservoir, numerically, is relatively small, particularly if resident training is included in our

TABLE III

NUMBER OF CASES REPORTED BY 22 MEMBERS OF SURGICAL ADVISORY COMMITTEE

Procedure	Number of Cases			
	Over 100	50 to 99	25 to 49	Under 25
Subclavian-Systemic Anast	4	7	3	8
Aortic-Pul Anast	2	1	2	14
Pul -Valvotomy	0	2	0	20
Infundibulectomy	0	0	1	9

TABLE IV
INCIDENCE OF RE-OPERATION

Number of Cases	Procedure	Re-Operated No	Re-Operated Per Cent
185	Subclav-Pul Anast	16	8 6
58	Aortic-Pul Anast	2	3 4
106	Pul Valvotomy	1	0 9
19	Infundibulectomy	4	21 0

thinking Not only teaching hospitals but many large and even some small community hospitals have taken the attitude that whatever is being done elsewhere should be done within their halls also, especially if it is dramatic and likely to stimulate further community support We cannot reasonably expect an automatic solution of the problems on the basis of the time honored law of supply and demand because in recent years this law has been rendered largely unreliable by distorting, powerful, artificial influences, most of which we, as physicians, have sponsored or have passively accepted

Re-operation after failure of an initial procedure was reported as being necessary in 0 9 per cent of the valvulotomy cases, with increasing frequency in the other groups up to a maximum of 21 per cent in those treated by infundibulectomy (Table IV)

The indications for re-operation were incomplete relief of right ventricular outflow tract obstruction or inadequate systemic-pulmonary artery shunt

II *Results of Surgical Treatment*

Clinical results classified simply as "good" or "poor" were reported in 1681 survivors Obviously, these descriptive terms are based upon the overall general condition of the patient and have no reference to future complications which probably will arise as a result of residual defects, any one of which may represent an indication for surgical correction (Table V)

Both shunt procedures gave essentially the same results, i e, approxi-

TABLE V
CLINICAL RESULTS (1681 SURVIVORS)

Number of Cases	Procedure	Result (Per Cent) Good	Result (Per Cent) Poor
1041	Subclav-Pul Anast	86 8	13 2
368	Aortic-Pul Anast	85 3	14 7
195	Pul Valvotomy	79 4	20 6
37	Infundibulectomy	75 6	24 4
40	Open Repair	100 0	0

TABLE VI

OPERATIVE MORTALITY RATES (VARIOUS TECHNIQUES)

Age	Number of Cases	Deaths Per Cent
Under 14 Years	261	16 0
Over 14 Years	60	23 3

mately 86 per cent "good" and 14 per cent "poor " The direct operations on the stenotic valve or infundibulum produced somewhat less favorable results with approximately 78 per cent listed as "good" and 22 per cent "poor " It is interesting and encouraging to note that the one surgical group reporting 58 cases treated by an open operation indicated the attainment of "good" results in 100 per cent of the survivors This would tend to dispel the fear that correction of the septal defect and removal of the right ventricular outflow tract obstruction at the same time might have an untoward effect on the pulmonary vasculature Significant data were not obtained concerning the frequency of "good" and "poor" postoperative results, initially, one year later, and five years following surgery

The effect of the patient's age on the results obtained was given in a small group of cases The mortality rate in those over 14 years of age was somewhat higher (23 3 per cent) than it was in those below 14 (16 per cent) (Table VI)

While the clinical impressions of some reporting surgeons indicated that the clinical results were better in patients under 14 years of age, still in the 230 cases where percentages were given, good results actually were somewhat more common in the older age group (Table VII)

III *Miscellaneous Data*

In 901 patients surviving surgery the incidence of subacute bacterial endocarditis or brain abscess was 1 5 per cent This relatively high incidence of serious bacterial complications is another significant factor which must be considered during our deliberations on indications for surgical treatment

The hematocrit, hemoglobin, or red blood cell count, returned to a normal range in only 23 3 per cent of 386 patients concerning whom this question was answered

TABLE VII

CLINICAL RESULTS (VARIOUS TECHNIQUES)

Age	Number of Cases	Per Cent Good	Per Cent Poor
Under 14 Years	200	78	22
Over 14 Years	30	81	19

The absence of a pulmonary artery which could be used in establishing an adequate shunt was reported in 4.3 per cent of 1033 cases.

Discussion

Offhand, the results of the various surgical measures used in treating the tetralogy of Fallot would seem quite satisfactory, especially if attention is focused on the reported percentages of "good" results which average around 75 to 85 per cent. However, these percentages are based solely upon the condition of those surviving surgery and its complications. The patients who died during the operation or later were excluded. If a more critical and realistic analysis is made, one must conclude that an average patient subjected to one of the standard operations is not justified in anticipating an 80 per cent chance of a "good" result with a 20 per cent chance that the result will be "poor." Actually, he must face a risk of 10 to 20 per cent that he will die within three months of the operation, another 2 to 6 per cent chance that he will die within the next five years or so and an additional risk of 15 to 25 per cent that he will obtain a "poor" clinical result. This may arise from such complications as uncontrollable pulmonary hypertension, cardiomegaly, progressive cardiac decompensation and important postoperative alterations of intrapericardial anatomy, etc., part or all of which may be irreparable even by definitive surgery at a later date. In summary then, his chance of obtaining a "good" result would be 61 per cent with a 39 per cent chance that he will die or obtain a "poor" result.

The relatively favorable results now reported in cases treated by the open technique presumably will be duplicated or improved upon in the near future. Therefore, it would seem reasonable to postpone surgery of any type unless proved satisfactory facilities for the open operation can be made available at a reasonable operative risk. Even if such facilities are not available, perhaps the complete operation should be reserved solely for those patients who show evidence of deterioration in their general condition, or for those whose course is static, but whose general condition is poor. As further experience actually reduces the operative risk, the surgical indications may be extended to patients who are doing well clinically, if operative units providing satisfactory results are accessible. Unfortunately, for various reasons, units providing for safe open heart surgery are not available at present for most patients with the tetralogy of Fallot and perhaps will not be available in many areas for some time to come. Therefore, one of the standard incomplete operations should be advised in patients who are showing definite evidence of deterioration from a clinical standpoint, and in those whose general condition is intolerably poor.

Conclusions

1. This report concerns an analysis of the results obtained in the surgical treatment of 4062 cases of the tetralogy of Fallot by 39 members of the Advisory Committee of The Section on Cardiovascular Surgery of The American College of Chest Physicians.

2 Although "good" results were reported in approximately 80 per cent of the patients surviving the various standard operations, still patients submitting to these procedures are actually faced with a 39 per cent risk of death or a "poor" clinical result

3 Complete open repair using cardiac by-pass techniques was reported by some as providing "good" results in most instances, with a total associated mortality rate approaching that of the standard incomplete techniques

4 The operative mortality rate associated with open techniques, as reported by most surgeons, was 95 per cent This indicates clearly that extreme caution should be exercised before any individual or group of individuals embarks upon the development and clinical employment of one of the cardiac by-pass techniques, and also indicates that the total number of these units in any geographic area should be kept as small as is practicable

5 In view of the evidence at hand, it would seem advisable to postpone all types of surgery in patients with the tetralogy of Fallot whose general condition is not poor or deteriorating, unless a safe facility for cardiac by pass and total correction of all the defects is available

6 If the patient's general clinical condition is poor or deteriorating, cardiac by-pass with complete correction of the defects should be done if safe facilities are available, but if not, one of the standard incomplete operations should be performed

AMERICAN COLLEGE OF CHEST PHYSICIANS

Section on Cardiovascular Surgery

Committee on Cardiovascular Disease

Charles P Bailey, Philadelphia, Pennsylvania — *Chairman*
Paul C Samson, Oakland, California — *Vice Chairman*
David H Waterman, Knoxville, Tennessee — *Secretary*
Richard J Bing, St Louis, Missouri
William R Rumel, Salt Lake City, Utah

Advisory Committee

Osler Abbott Emory University Georgia
Ralph Adams Wolfeboro New Hampshire
Henry Bahnson Baltimore Maryland
Charles P Bailey Philadelphia Pennsylvania
Howard John Borrie Dunnedin New Zealand
Claude S Beck Cleveland Ohio
W G Bigelow Toronto Canada
H H Bradshaw Washington D C
Otto C Brantigan Baltimore Maryland
Mario M Brea Buenos Aires Argentina
C J Officer Brown Victoria Australia
William S Conklin Portland Oregon
Edgar W Davis Washington D C
E Derra Dusseldorf Germany
F Dewey Dodrill Detroit Michigan
L D Eerland Groningen Netherlands
Leif Efskin Oslo Norway
Gunnar Ekstrom Stockholm Sweden
Egbert H Fell Chicago Illinois
John H Gibbon Philadelphia Pennsylvania
Robert P Glover Philadelphia Pennsylvania
Alfred Goldman Beverly Hills California
Robert E Gross Brookline Massachusetts
John B Grow Denver Colorado
C Rollins Hanlon St Louis Missouri
Jose Hilario Rio De Janeiro Brazil
Charles A Hufnagel Washington D C
Ormand C Julian Chicago Illinois
Pietro Valdoni Rome Italy
Arthur Vineberg Montreal Canada
E J Zerbini Sao Paulo Brazil
Earle B Kay Cleveland Ohio
Edward M Kent Philadelphia Pennsylvania
John W Kirklin Rochester Minnesota
Rodolfo Kreutzer Buenos Aires Argentina
Conrad R Lam Detroit Michigan
Jere W Lord Jr New York City
Laurence Miscal New York City
William H Muller Charlottesville Virginia
Gordon Murray Toronto Canada
Rowen Nicks Auckland N Zealand
Ross Robertson Vancouver Canada
Clemente Robles Lomas Mexico
William R Rumel Salt Lake City Utah
Paul C Samson Oakland California
Paul Santy Lyon France
William Scott Jr Nashville Tennessee
W C Saely Durham N Carolina
Marceu Servelle Paris France
Robert R Shaw Dallas Texas
D Arcy Sutherland Adelaide Australia
Henry Swan Denver Colorado
Arthur S W Touroff New York City
Richard L Varco Minneapolis Minnesota
David Waterman Knoxville Tennessee
Harry Windsor Sydney Australia

Editorial

Biological Effects of Diagnostic X-rays*

For years increasing use has been made of radiologic examination of the chest both for individual diagnosis and for mass screening for disease as a means of protection of the community As is not infrequently the case with a useful procedure, it may tend to be overdone The Committee on Radiation Effects of the National Academy of Sciences called attention in the spring of 1956 to the amounts of radiation received by the gonads in the course of the diagnostic use of radiation and called attention to the fact that the total dose to the gonads was in some countries approaching a level of genetic significance to the race Their findings were reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation which made in a statement distributed to medical journals the following significant points among others

"The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease, but the possible effects of this irradiation of individuals require examination the extent of such genetic radiation from diagnostic procedures has been found to be equal to at least 100 per cent of all natural radiation in two countries The Committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods In particular it would be valuable to know how much the radiation to the gonads could be reduced"

That the fears of the geneticists are not entirely academic and that even the risk of somatic damage in some diagnostic procedures is real is evidenced by the following experience of a patient in a sanatorium in the United States In one month he received diagnostic radiologic examinations that delivered to his skin and that portion of his bone marrow close to his skin a total of 70 r

It is important that radiation be used with caution and economy of exposure, but it is equally important that we not allow such diseases as tuberculosis and operable cancer of the lung to be missed until they have become virtually incurable

It should be remembered, particularly in the case of children, that skin testing for tuberculosis is in many communities a satisfactory mass screening method, only the positive reactors being subjected to x-ray examination

The present estimate based on studies made for the National Academy of Sciences Radiation Committees is that males receive 1 2 milliroentgens in a diagnostic chest examination, females 0 3 milliroentgens The effect on the gonads is cumulative, and there is no threshold, so any added radiation at the natural background radiation must be considered as damaging

---

*From the Cancer Research Institute, New England Deaconess Hospital, Boston

in slight degree Geneticists have agreed that in general it is feasible for a population to receive an average dose to the gonads of 10 r up to age 30 in addition to the approximately 10 r that they have received during the same time from the natural background radiation The level at which damage is done to bone marrow is as yet uncertain, but 15 r to the whole body or to the bulk of the skeleton will produce transient though insignificant changes in the white blood cells It is probable that the increased incidence of leukemia in radiologists is associated with an accumulated dose of close to 1000 r

If each physician would ask himself before ordering a diagnostic procedure, "Is this really necessary," much unessential radiation could be avoided At the same time the value of mass screening techniques for the detection of tuberculosis and other lesions of the lung is sufficiently high to regard a discontinuance or impairment of them as a public health disaster

It is feasible to utilize x-rays safely but constant vigilance must be maintained to prevent unnecessary frequency of diagnostic examinations and undue exposure in the course of diagnosis

SHIELDS WARREN, M D *
Boston, Massachusetts

*Consultant, U S Atomic Energy Commission U S Representative on the United Nations Scientific Committee on the Effects of Atomic Radiation Professor of Pathology, Harvard Medical School at the New England Deaconess Hospital

Tuberculosis Control in the Philippines and International Congresses

Our discussion of the campaign against tuberculosis in the Philippines inevitably concerns itself chiefly with local conditions We feel that although the observations come from an isolated sector, they are not only of pathetic interest because of the extreme difficulties encountered and the heavy inroads which the disease makes on our poor community, but also because of their international implications As has been said, "no nation is safe if another nation is vanquished by the disease" Tuberculosis has been for centuries the number one disease in this country and bids fair to continue so for many a decade yet to come

The organized campaign against tuberculosis in the Philippines was initiated under the patronage of the Governor-General and other high government officials some 45 years ago, but it was largely promoted and maintained by private voluntary agencies, aided subsequently by fund-raising legislation, like the enactment of the Philippine Charity Sweepstakes The campaign against tuberculosis is the longest sustained campaign and one of the greatest voluntary efforts against a single disease in the history of this country This circumstance alone is of the greatest importance because it enhances community interest in health matters, particularly with reference to this number one disease, and the movement should be encouraged if only for that consideration We are still far from being genuinely health minded

Because of low economic conditions, it is almost a derision to speak of home or domiciliary treatment in the Philippines, if that term implies any sense of home adequacy Serious efforts are being made in this direction, mainly because of highly inadequate hospital facilities The homes of our poor are tiny one-room, or at best two-room affairs, where everybody in the household lives, moves about and sleeps, in sickness and in health Remembering that it is not unusual for several families to constitute the Filipino household and that the average Filipino family is proverbially a large one, this gives an idea of the terrible exposure to which the many contacts are exposed This is only to point out the difficulties and the scant results that can be expected from such measures The educational efforts must therefore be continued with vigor and purpose

When we read about the recent trends in the treatment of tuberculosis with emphasis on home or domiciliary treatment, we can only feel the bitterness and pathos of it in the light of our local conditions Nothing radical can be accomplished in this direction until the overall economic status of our people materially improves It will always remain an uphill fight to bring this about without seriously endeavoring to change the sense of values of our people by precept and example

Another prolific source of spreading tuberculosis infection in our community is the fairly large number of public school teachers who, even though they are supposed to be x-rayed and screened before employment

and examined periodically during employment, are found to have advanced lesions after having taught for long periods, and exposing an average of 40 to 80 children daily, depending upon whether they have single or double sessions The results staggeer the imagination In the case of private school teachers the situation is probably worse

If these things happen with groups that are at a high instructional level, how much less satisfactory must be the conditions elsewhere Furthermore, the problem of tuberculosis definitely calls for a more prominent place in the teaching in medical schools of this country

These are instances of the inadequateness of attention given to the problem of controlling tuberculosis in this country Voluntary agencies, such as the Philippine Tuberculosis Society, have definitely been helping the Government a great deal for many years and should be given the utmost encouragement and recognition

In this connection, the personal contacts made at the International Congresses on Diseases of the Chest held in Rome, Rio de Janeiro, Barcelona and Cologne—like the First Pacific Conference on Tuberculosis which was held in Manila four years ago, and the XIVth International Union Conference on Tuberculosis held recently, in New Delhi, India—have been of incalculable value to tuberculosis workers in the Philippines To these must be added the much sought for visits to this country by recognized authorities in the campaign against tuberculosis

MIGUEL CANIZARES, M D , F C C P
Manila, Philippines

---

*Regent for the Philippines

J Winthrop Peabody, Sr , M D

DR J WINTHROP PEABODY, SR RECEIVES 1958 COLLEGE MEDAL

Dr J Winthrop Peabody, Past President of the American College of Chest Physicians, was presented with the College Medal and Certificate of Award for meritorious achievement in the specialty of diseases of the chest at the annual meeting of the College in San Francisco, California, on June 21, 1958 The award was made by Dr Burgess L Gordon at the President's banquet held at the Fairmont Hotel

The award was given in recognition of Dr Peabody's unselfish devotion to the aims and ideals of the College since its foundation, but particularly to the advancement of postgraduate medical education Since its inception in 1946 he has served as Chairman of the Council on Postgraduate Medical Education of the College, and during the 12 years intervening has the unique record of having organized and participated in 54 Postgraduate Courses in 14 cities with 3,704 physicians in attendance

Dr Peabody's interest in medical education began as Instructor of Medicine in 1921 at Georgetown University School of Medicine and later as Professor of Diseases of the Respiratory System In 1951 he was awarded the Vicennial Medal for long and distinguished service He was elected Emeritus Professor in 1957—marking 36 years of continuous teaching in the University He is an alumnus member of Alpha Omega Alpha Honor Medical Society, Georgetown University

As Superintendent of the Tuberculosis Hospital (1921-1934), Washington, D C, and later as Medical Director of the new modern institution at Glenn Dale, Maryland, Dr Peabody has constantly worked toward better care for the tuberculous patients in the District of Columbia In 1953 he was awarded a certificate of merit by the Department of Public Health for 37 years of efficient service

Dr Peabody has been actively identified with the District of Columbia Tuberculosis Association since 1921—serving as President 1939-1943 He has been a member of the Board of Directors of the National Tuberculosis Association for many years, and is presently a member of the Advisory Council, American Trudeau Society

He served as first Chairman of the Section on Diseases of the Chest, American Medical Association, which was organized in 1952 and is presently the Alternate Delegate from the Section to the House of Delegates of the American Medical Association He is an Associate Editor of the journal, *Diseases of the Chest*, author of many editorials and papers on diseases of the chest and a contributor to several textbooks

Dr Peabody is a Diplomate of the American Board of Internal Medicine, and holds membership in many local, national, and international medical societies He serves as Civilian Consultant in Diseases of the Chest at the U S National Naval Medical Center, Bethesda, Maryland and Glenn Dale, Maryland

Donald R McKay, M D

President

1958-1959

DR DONALD R McKAY

Takes Office as College President

Dr McKay, Buffalo, New York, was born on February 22, 1898 in Sunnidale, Ontario, Canada He graduated from the University of Toronto, Faculty of Medicine in 1925 Internship was served at the Buffalo City Hospital, later called the E J Meyer Memorial Hospital in Buffalo, New York The following year was spent on the Obstetrics and Gynecology service before he decided on a medical career He served as Assistant Resident in Medicine and later Resident in Medicine on the Tuberculosis Service of the E J Meyer Memorial Hospital and is presently Chief Attending Physician on this service Since this Hospital is one of the teaching facilities of the University of Buffalo Medical School, he early became a member of the teaching staff, and presently is an Associate Clinical Professor of Medicine

Other hospital affiliations include Attending Physician at the Millard Fillmore Hospital, another affiliate of the University of Buffalo Medical School and Consultant Physician at several other Western New York area hospitals, including the Veterans Administration Hospital in Buffalo and the New York State Hospital at Gowanda

He has been a member of the American College of Chest Physicians since the formation of the New York State Chapter in 1941, serving as Secretary-Treasurer of the Chapter for four years Later he became Regent of the College for New York, Regent at Large, Chairman of the Board of Regents and member of the Executive Council He was elected Vice President in 1955

Other medical associations include Fellowship in the American Medical Association, the New York State Medical Society, the Erie County Medical Society, a life member of the American College of Physicians, a member of the Trudeau Society, the New York State Society of Internal Medicine, the American Heart Association, the American Public Health Association and the Buffalo Academy of Medicine

He has been a director of the Buffalo and Erie County Tuberculosis Association for nearly twenty years and President of the organization for the past five years He is a director at large of the New York State Committee of Tuberculosis and Public Health He is a past president of the Millard Fillmore Hospital Medical Staff, the E J Meyer Memorial Hospital Medical Staff and the Buffalo Academy of Medicine

He has written or collaborated in writing several papers relating to pulmonary diseases

Other interests include membership in several civic and fraternal organizations

Dr McKay and his wife Jessie G reside in Eggertsville, New York, a suburb of Buffalo

College Chapter News

MINNESOTA CHAPTER

The Minnesota Chapter will hold its annual meeting at Pine Beach Hotel on beautiful Gull Lake, Brainerd, Minnesota Labor Day weekend All College members and their families are invited In addition to the interesting scientific program there will be bathing, water skiing, fishing, golf, horseback riding and special events for children Write directly to the hotel for further information and reservations

NEW CHAPTER OFFICERS

ARIZONA CHAPTER

President	William B Steen, Tucson
Vice-President	Lloyd K Swasey, Phoenix
Secretary-Treasurer	Bertram L Snyder, Phoenix

ILLINOIS CHAPTER

President	Robert T Fox Evanston
President-Elect	George H Vernon, Edwardsville
Vice-President	Gordon L Snider, Chicago
Secretary-Treasurer	Samson D Entin, Chicago

MISSISSIPPI CHAPTER

President	Thurman T Justice, Jr , Gulfport
Vice-President	Robert Neil Brown, Jackson
Secretary-Treasurer	Lee R Reid, Jackson

NEW JERSEY CHAPTER

President	Lewis Baum, South Orange
President-Elect	Arthur Bernstein, Newark
Vice-President	A A Carabelli, Trenton
Secretary-Treasurer	Emanuel Klosk, Newark

NEW YORK STATE CHAPTER

President	Emil A Naclerio, New York City
1st Vice-President	Henry W Leetch, Saranac Lake
2nd Vice-President	Willard J Davies, Rockville Center
Secretary-Treasurer	Harry Golembe, Liberty (re-elected)

PHILIPPINE CHAPTER

President	Jose Celis, Quezon City
President-Elect	Manuel Quisumbing, Sr , San Pablo City
Vice-President	Alejandro Sanchez Gaerlan, Manila
Secretary	Priscilla J Tablan Quezon City (re-elected)

SOUTHERN CHAPTER OF SOUTH AFRICA

President	David P Marais, Cape Town
Vice-President	Theodore Schrire, Cape Town
Secretary	Hendrik Muller, Cape Town
Treasurer	Michael J Bailey, Cape Town

ERRATUM

We wish to call your attention to an error which appeared on page 420 in the April issue in a paper entitled "The Occurrence of Arrhythmias in Acute Myocardial Infarctions" The paper contained the statement "The authors believe that both digitalis and quinidine are contraindicated in the presence of complete heart block" which should have read "The authors believe that quinidine is contraindicated in the presence of complete heart block"

DISEASES of the CHEST

VOLUME XXXIV AUGUST, 1958 NUMBER 2

Pathologic Findings in Benign Pulmonary Histoplasmosis*

Preliminary Report—Part I†

HENRY C SWEANY, M D, F C C P,** DAVID GORELICK, M D,‡
FRED C COLLER, M D‡ and JAMES L JONES, H T§
Mt Vernon, Missouri

Owing to its close mimicry of other diseases, histoplasmosis has escaped recognition as a common disease entity until about the last 15 years After Darling's first report[1] in 1906, it was almost three decades before the full significance of his discovery was realized The more important advances in the history of the disease have been given recently by Schwarz and Baum[2] Without going into details, therefore, let it be stated that there have been several types of disease recognized ranging from the generalized and fulminating form to those with no symptom at all The severe type was described by Darling and was considered by him and his immediate successors as almost always fatal Although this type was uncommon, it probably was present under a masquerade of a rare septicemia or anemia The various other clinical types of the disease have been given recently by Furcolow,[3] which are listed as the asymptomatic, mild, moderately severe, and severe types, with various subgroupings One of the important aspects mentioned was the close similarity to tuberculosis

Since this is primarily a pathologic study, the discussions will be confined chiefly to methods of identifying the disease and to pathology The fulminating type of disease has been well documented by Darling and others Generally there is reported a great profusion of histiocytes which are packed with small, round or oblong bodies having a small nucleus The close resemblance to Kala-azar has been mentioned by Darling[4] and by Meleney[5] One of the characteristics of this type of lesion is that it is almost purely a histiocytic reaction with no polymorphs, lymphocytes,

*From the Missouri State Sanatorium We are deeply indebted to Dr Charles A Brasher, Medical Director, for unreserved support in this work

It was the privilege and pleasure of one of us (S) to be accorded the courtesy of members of the Armed Forces Institute of Pathology, in Washington, D C, where many valuable suggestions were made that helped to orient us in our studies We are particularly grateful to Capt Silliphant, Director of the Institute, and to Dr S H Rosen, of the Pathological Department of Chest Diseases

**Director of Research, Pathology and Allied Sciences

†Presented in brief before the Chicago Pathological Society, May 13, 1957, and in full at the Am Soc Clin Path at New Orleans, Oct 2, 1957

‡Consulting Pathologist

§Histological Technician

A few specimens were from the Pathology Department of St John's Hospital and Springfield Baptist Hospital, Springfield, Mo, where D G and F C are pathologists

Copyright 1958 by the American College of Chest Physicians

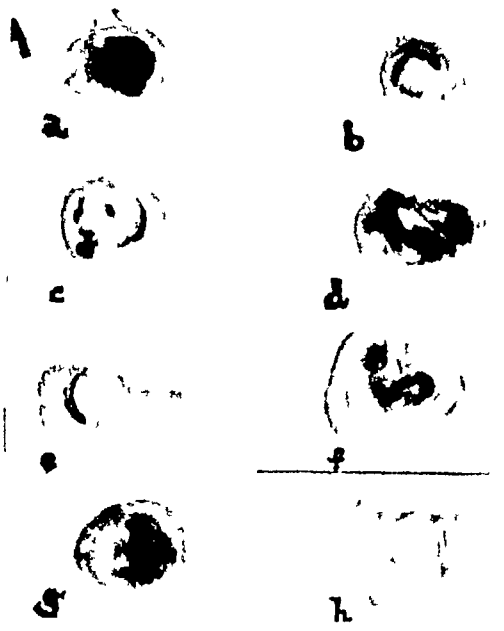


FIGURE 1

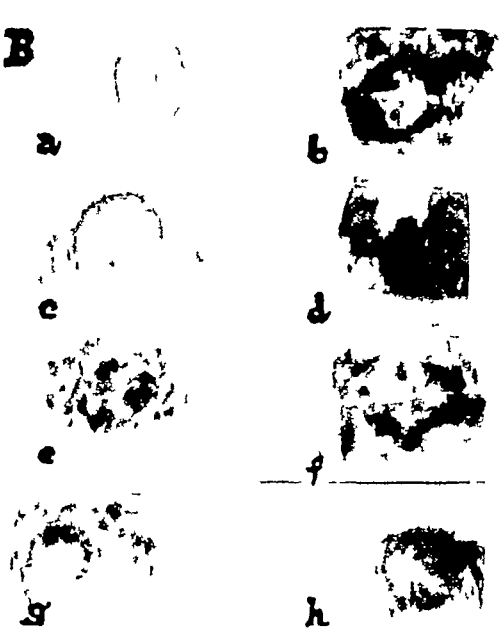


FIGURE 2

Figure 1 This is designated as A which represents typical histoplasmomas They are to be contrasted with typical tuberculomas which are found in the B group H & E Stain a M S, A20—No 24,674, is the stained section of a 1½ mm spherical lesion from the lung parenchyma of a 57 year old housewife, negative tuberculin, strongly positive histo skin reaction Numerous yeast-like bodies were found b N O, A30—No 26,079, similar section from a 2½ cm spherical lesion taken from the lung parenchyma of a 51 year old housewife Both tuberculin and histo skin tests were strongly positive Innumerable yeast bodies were found in the central part of the lesion c E S, A15—No 24,493, similar section from the lung parenchyma of a 49 year old housewife Tuberculin test was weakly positive, histo skin test strongly positive Large number of yeast bodies were found d M B, A23—No 25,217, similar section from a 46 year old housewife Tuberculin test weakly positive, histo skin test slightly more positive Many yeast bodies found in the lesion e H S, A9—No 23,517, a 61 year old carpenter Tuberculin weakly positive, histo strongly positive Many yeast bodies found f L B, A21—No 24,797, from the parenchyma of a 44 year old housewife Tuberculin negative, histo skin test weakly positive A few yeast bodies were found g O I, A12—No 24,302, was the same from a 42 year old truck driver Tuberculin and histo skin tests were both weakly positive There were many yeast bodies found h W F, A41—No S-0591 from St John's Hospital This is a 52 year old white male having lesion discovered on routine x-ray A few typical yeast bodies were found —*Figure 2* Designated as B, represents 8 spherical lesions in which acid fast bacilli have been found and no yeast bodies a A47—No X-117 from a 40 year old male taken many years ago in Chicago This was a lesion quite similar to many of the lesions found in histoplasmosis It seemed to have been built up from a central focus Acid fast bacilli were found in the periphery It shows that the two diseases run parallel in many respects However, there are many more of this type that are histoplasmosis than are tuberculous Another point is that in the center of the lesion the parasites of histoplasmosis appear to live longer and produce more caseation and calcification with actual growth of the parasites, whereas tubercle bacilli are usually smothered after a few years b B S, A11—No 23,701, a spherical lesion from a 19 year old housewife Weakly positive tuberculin, negative histo skin reaction Acid fast bacilli found c C J, A14—No 26,118, from a 37 year old cafe manager Both tuberculin and histo skin tests were positive Acid fast bacilli were found d G P, A16—No 24,645, from a 46 year old housewife Tuberculin strongly positive, histo not done Many acid fast bacilli found e C P, A6—No 22,584, a 45 year old farmer, strongly positive tuberculin, histo not done Many acid fast bacilli found f A larger section from another spherical lesion in the same patient, in which AFB were found g I C, A5—No 22,206, strongly positive tuberculin, histo test not done Many acid fast bacilli were found h F A, A25—No 25,057, skin test, tuberculin negative Histo skin test weakly positive Section from spherical lesion of a 38 year old housewife Acid fast bacilli found The A and B in these two figures are not to be confused with the same letters in the two main groups

plasma cells, or other characteristics of an acute infectious process The histiocytes of the lung, liver, spleen and lymph nodes of the body become packed with the dot-like forms that may be seen on almost any stain, but are sometimes easier to see when stained with the periodic acid of Schiff (P A S) as used by Bauer,[5] later modified by Hotchkiss and McManus,[7] or Gridley's stain[8] The Gomori method,[9] however, as recently applied by Grocott[10] to mycological forms, is far superior to all others tried up to this time As the disease progresses and the circulation becomes shut off, caseation develops and where the focus approaches the bronchus, cavities may form The lymphatics are always invaded The blood vessels are nearly always penetrated resulting in a hematogenous dissemination involving the spleen, adrenals, liver, bone marrow and lymphatics The best illustration of the fulminating infection is that seen in the mouse where the histiocytes are packed with yeast and many of the organs may be 10 to 20 times their normal size More recently the pathology of various types of the disease has been given by Schwarz,[11] Meleney,[4] Pinkerton,[12] and especially Binford[14]

Material[*]

Our material consists of two clinical types first, clinically inactive, circumscribed lesions (so-called "coin" lesions), and second, obviously clinically active disease As will be seen later there are few if any cases with yeasts present even in encapsulated lesions that are completely inactive Along with the definitely positive cases there were almost as many which were suspected of histoplasmosis at one time or another or were similar in appearance to the other lesions and which serve as controls

In the first, or group A, as subsequently designated, there were 21 proven cases of histoplasmosis (Six more have been found since this was written) There were 11 others in which acid-fast bacilli were found in the sputum or on the excised specimens Of the other five, one case had a typical primary tuberculous complex with a strongly positive tuberculin and a negative histo skin reaction Of the other four cases, three were probably histo, and one was undetermined, but was considered tuberculous in spite of a negative A F B stain

In Group B with clinically active disease, there were 16 cases positive for histoplasmosis by the staining method (Eleven more have been found since this was written) In 11 cases acid-fast bacilli were found either in the sputum before operation, or in the tissues after operation, or both (*Four of these 11 had both acid-fast bacilli and H capsulatum*) One case had acid-fast bacilli and may also have had occult histoplasmosis, but no yeast bodies were found There were three cases in doubt, but they had more evidence in favor of histoplasmosis than tuberculosis There were three having a diagnosis of bronchogenic carcinoma in which no H capsulatum were found on stained section One case in particular that was classed as a "granuloma" had a strong histoplasmosis complement fixation

*All but three postmortem specimens were obtained from surgical resections performed by Dr John W Polk, Chief Surgeon, Dr W W Buckingham, Chief Surgical Consultant, and Dr Jose Cubiles, Chief Surgical Resident

FIG 3

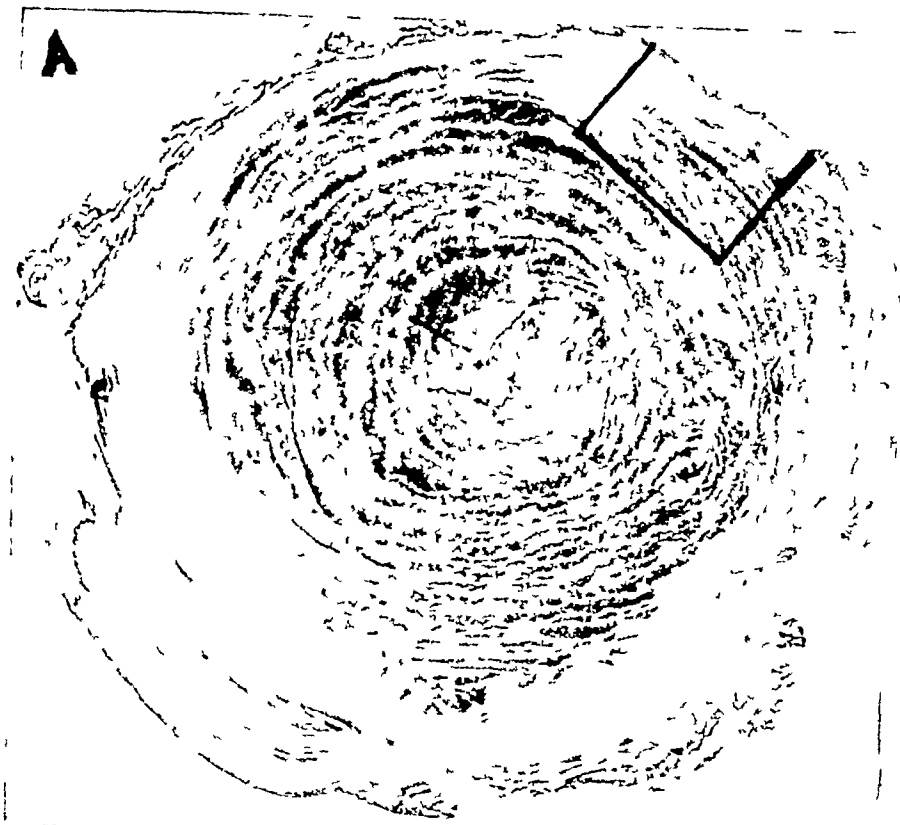


FIG 4

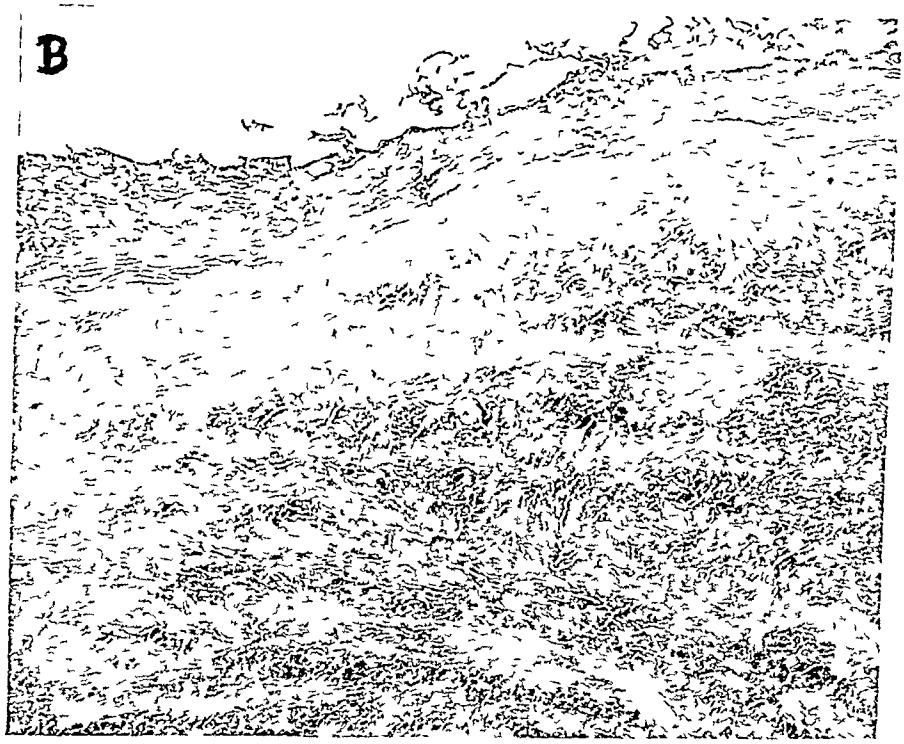


Figure 3 (A) A stained section of a spherical lesion of M S, A39, S2037-55, showing the ring formation from the center outward Note the heavy callous on one side This heavy button-like plaque on one side is present on several spherical lesions and its cause is not understood H & E × 45—*Figure 4* (B) A higher magnification of area marked off in Fig 3 The calcification does not follow the fibrils, but is more related to distance from the center H & E × 20

reaction Although the complement fixation reaction has been misleading in many cases, we feel that in this instance, where the reaction was present in a dilution of 1 128, the diagnosis of histoplasmosis was probably correct, but the case remained in the doubtful group

Pathology

Since the material at our command is quite extensive, the present study will be in the nature of a preliminary report embracing the methods of study, tracing the course of the parasite in the body and roughly classifying the material in provisional groups, with a few illustrations of certain important features In later studies we hope to describe the material more completely

First are the circumscribed lesions that have sometimes been poorly designated as "coin lesions" because of the nummular appearance of the shadows on x-ray film and which may be considered under two headings for convenience those that develop centrifugally from a small central focus, and those that are encapsulated infiltrates with a larger early localization of the infection The third group consists of nodular lesions where the appearance ranges from a soft granuloma to fibrocaseous, calcific and calcific-ossified lesions The fourth group is chronic pneumonitis with an early histiocytic infiltration and an early organizing fibrinous exudate which later develops into a granulomatous process with epithelioid cell proliferation and Langhan's giant cells The fifth group consists of ulcerative lesions, acute caseo-ulcerative and fibroid, the latter with either cystic or dense cavity walls The sixth group is bronchiectasis The seventh is a pleuritic involvement Finally, there is a mixed type of one or more of these various forms

Descriptions of most of these eight groups will be given with a few illustrations

The group of circumscribed lesions, although similar on x-ray film appearance, is quite varied on gross and microscopic appearance There are at least two distinct types with several variations, depending on the development of the particular lesion One definite type is the centrifugally-formed lesions which slowly spreads from a small focus and builds up around the edges like the layers of an onion Sometimes the original focus may be found from which the process emanated The low resistance of the host, or a special virulence of the parasite, or both, has accounted for the gradual formation of lesions, sometimes 3-4 cms in diameter Inasmuch as there are so many of these circumscribed forms in histoplasmosis, it is a fair index of the general sluggish but tenacious nature of the parasites in the human body in the chronic forms of the disease

In the development of this lesion there are frequently alternating bands of fibrous tissue, one band containing many strands of long fibrils that are usually straight and encircle the focus Next to this lies irregularly-formed tortuous fibrocytes of varying thickness and containing much collagen These fibrocytes tend to undergo an early caseation and take on calcification giving the H and E stained section the laminated appearance of alternat-

ing dark and pink bands Sometimes pockets of caseation may appear instead of the laminations Whether the caseation is due to occult parasites or microsporoes of some type, or whether it develops as a result of a shut-

FIGURE 5

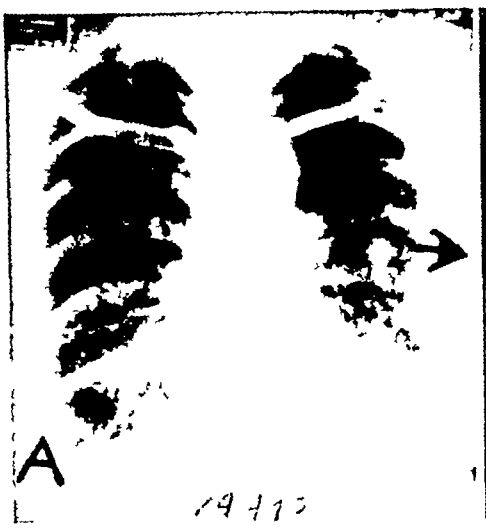


FIGURE 6

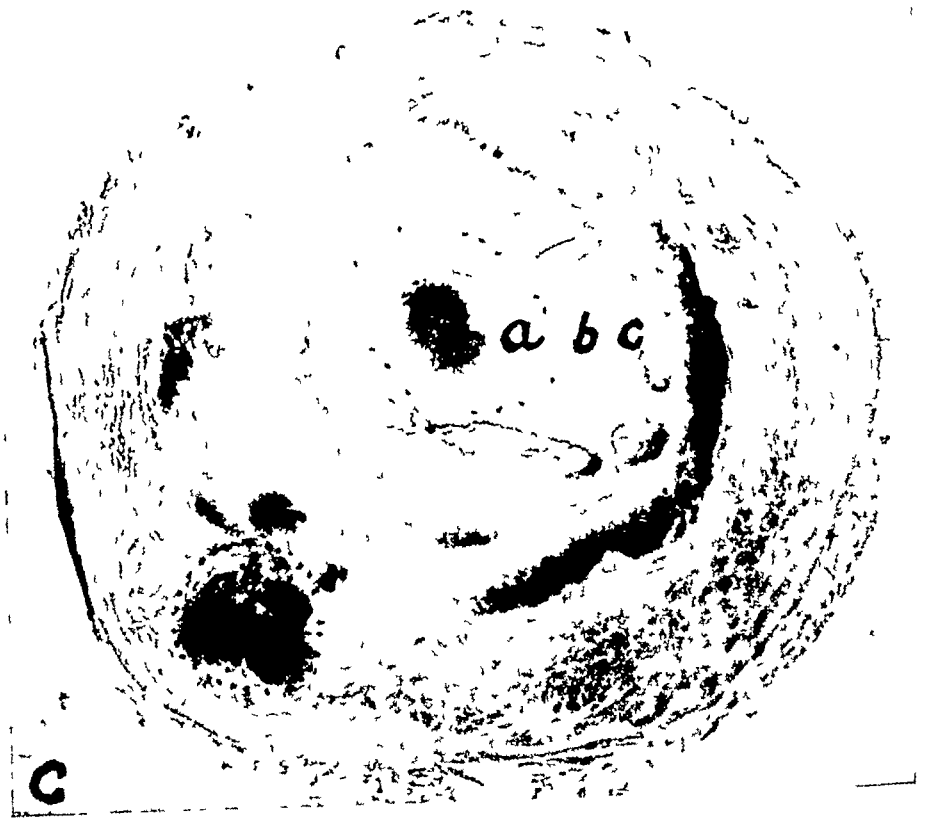


FIGURE 7

Figure 5 (A) A reduced roentgenogram of E L S, A-15, No 24,493 Showing a spherical lesion in the left midfield with pleuritis at the left base and bronchiectasis in the right middle lobe—*Figure 6* (B) An enlargement of the spherical lesion of Fig 5—*Figure 7* (C) A low power section of spherical lesion Note the two centers of dense caseation and calcification outlined by small dots at a and a' and the partial rings of less marked calcification

ting-off of the circulation with death of the fibrocytes, is problematical The fact is, that in most of these caseous foci are found the grayish-lavender stained bodies with the Gomori stain that are considered to be H capsulatum In this series, unless there were budding forms, a positive result was not recorded until a dozen or more of these stained bodies were found There were several of these spherical lesions in which no caseation could be found and no parasites Almost invariably the parasites were found only in caseous foci In two lesions only three or four suspicious bodies were found It was thought highly probable that some of them were the parasites of histoplasmosis, but there was not enough evidence for a certain diagnosis, and they were not counted as histoplasmosis

Almost identical lesions are found in tuberculosis, although the "onion-ring formation" seems to be more pronounced in histoplasmosis—at least the true tuberculomata in this series were more homogeneous and less laminated, and had a greater tendency to ulceration The differences are too slight to afford a dependable means of differentiating tuberculoma from histoplasmoma The contrast of the two diseases is shown in figures 1 and 2

Two histoplasmoma type lesions will be described, the first of a typical "onion-peel" formation

M S A 41 S2037-55 The patient is a 52 year old white woman who entered St John's Hospital on August 27, 1955 In 1952 she had a thyroidectomy done and stated that she had had a cough ever since this operation She has also had hoarseness three months following the surgery In May of 1955, an x-ray film was made and she was found to have a mass in the right upper lung field She was advised to have surgery, but refused She enters the hospital at this time for surgery The physical examination revealed a well-healed thyroid scar with her cardiorespiratory system being negative However, there was possibly a soft systolic murmur present at the apex The balance of the physical examination was negative At surgery a 6 cm "tuberculoma" was found lying in the posterior segment of the right upper lobe This was removed in a wedge resection The mass measured 4 x 3 x 3 cm It was extremely hard and also contained a gray-white plaque on the external surface The plaque measured 12 x 10 mm Beneath it there was a rounded tumor mass measuring 2 cm in diameter It contained a soft, central yellowish-gray core Around this there were grayish-yellow laminations The microscopic examination revealed a central area of calcified material with a wall of dense fibrous tissue No cellular reaction was noted There was occasionally a few lymphocytes seen The adjacent pulmonary tissue was not remarkable Diagnosis "Tuberculoma" of the right upper lobe of the lung

Comment This case has every gross and microscopic characteristic of histoplasmosis, yet no yeast bodies were ever found There was apparently a beginning focus near the center with a gradual build-up around the periphery, like winding a ball of twine One outstanding feature, and one that may account for the absence of yeast bodies, was the absence of pockets of dense caseation If yeasts were present, we did not find them, but it has been explained that a section 6 μ thick represents only about one two-thousandths of the whole mass There may not have been the right conditions for formation of the caseation and consequently the "awakening" of the yeast bodies The reason for the dense fibrosis on one side is not apparent This was described as a "plaque 10x12 mm" This case is classed as a doubtful case, but from all appearances and past experiences in observing a large number of lesions it is probably histoplasmosis, since it is typical in every way except the presence of parasites

At the present time we have no concrete answer to the question of why

these lesions do not show parasites yet they keep on expanding There is something still lacking in our methods and in our knowledge of the disease

FIGURE 8

FIGURE 9

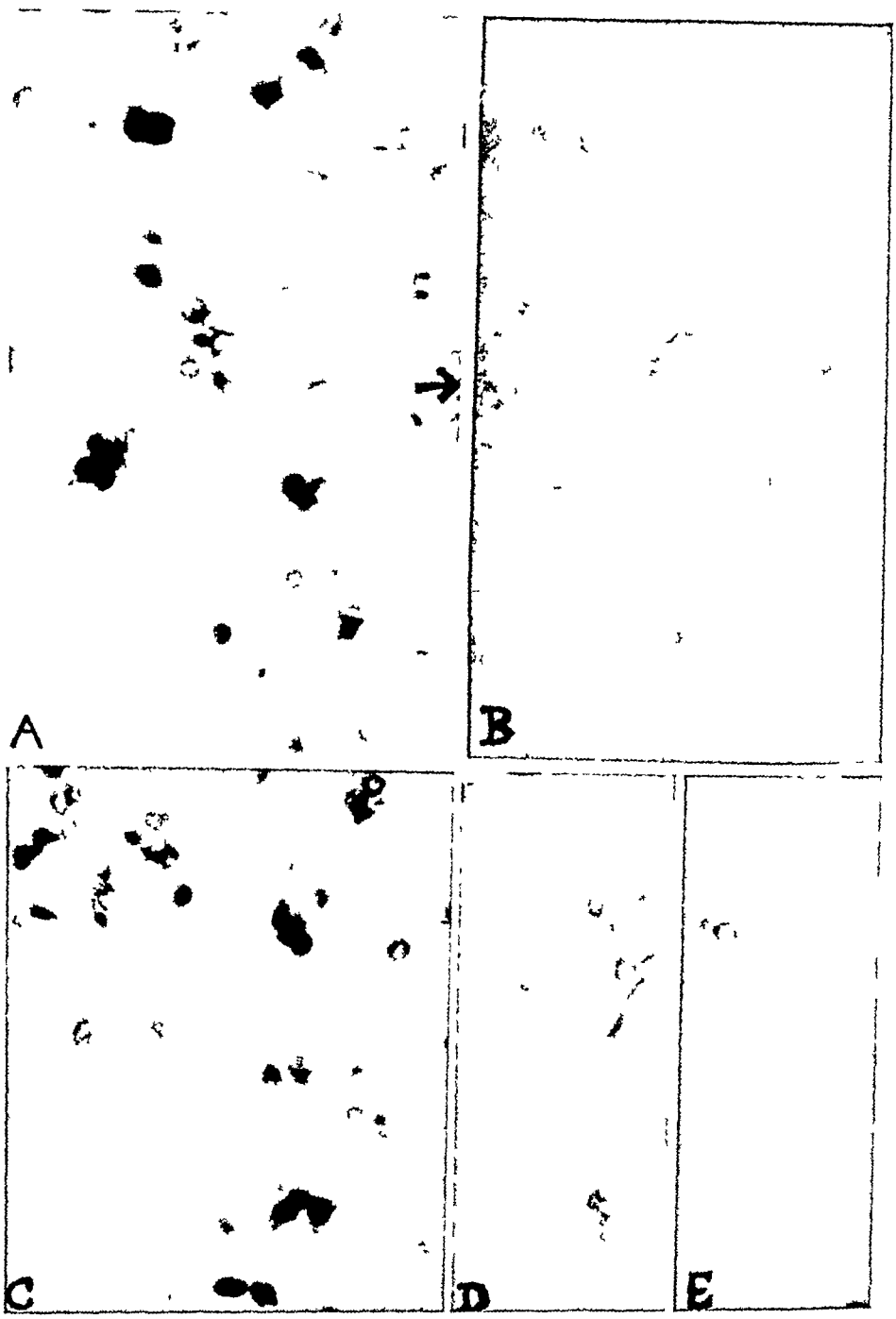


FIGURE 10 FIGURE 11 FIGURE 12

Figure 8 (A) A microscopic field of a G M S stained section in the dense central, calcification marked at "a" in Fig 7, showing innumerable yeast bodies × 3400— *Figure 9* (B) A polariscopic view of same, showing "Maltese crosses" × 3400— *Figure 10* (C) A microscopic field of stained section extending outward into the zone marked "b" in Fig 7 G M S stain × 3400—*Figure 11* (D) A microscopic field of stained section still further out toward the periphery—*Figure 12* (E) Similar to Fig (D)

The Von Kossa calcium stain only exaggerated the findings observed on the H and E stain There was no indication of an alveolar pattern as in the next case to be shown The Von Kossa stain divides the field into the expanding type from one that represented an entrapped infiltrate

Encapsulated infiltrates have an entirely different origin and appearance These lesions are made up of pockets of caseation which probably emanated from larger collections of histocytes laden with parasites Various fibrous bands separate many of these caseous foci in the central part of the lesion and around the periphery is a heavy layer of dense fibrous tissue that circumscribes the whole mass Some of these may be the parenchymal forms of a primary lesion Typical of this type is shown in the next case, Figs 5, 6 and 7

E L S A-15 No 24,493, was a 49 year old Pemiscot County housewife She was exposed to a son who had tuberculosis She was admitted to the hospital on February 27, 1955

Her histo skin test was positive 12/15 (12 mm induration, 15 mm erythema), weakly positive (3/5) for tuberculosis All complement fixation tests for histoplasmosis were negative All sputums were negative for acid fast bacilli and H capsulatum The X-ray film revealed a slight effusion at the left base and a spherical lesion in the left midfield of about 3 cm in diameter There also was found moderate bronchiectasis in the right middle lobe A wedge resection was performed on April 12, 1955 to remove the dense round lesion

The pathological examination revealed a solid fibroid mass 2-3 cm in diameter There was a slight softening with some calcifications in the center

A G M S stain revealed a remarkable distribution of many yeast bodies in the centers that showed the most caseation and calcification There were hundreds in the central area with a diminishing number outward to the fibrous tissue There were no full sized forms out near the margin, but many small forms measuring as small as 0 5 μ that polarized light and many still smaller that did not produce the usual Maltese cross on polarization Some showed only a point of light, others showed nothing A small focus of dense calcification out from the center revealed many budding parasites, but there were not as many as were in the central focus The lighter crescent of calcification did not show any forms, large or small

Comment It is difficult to say what is the course of events in this type of lesion From the appearance, however, it seems that the fibrous tissue becomes shut off from nourishment and gradually undergoes a chemical disintegration and caseation Calcium ions slowly penetrate the mass and produce the insoluble calcium soaps in the form of a calcified matrix of varying degrees of density depending perhaps on the age of the process

There appears to come a time when the conditions are suitable for the growth of the yeast bodies so that any dormant forms that were trapped at an earlier time will become active From numerous observations these forms begin as small black ring bodies (approximately 0 5 μ in diameter) and gradually enlarge to 2, 3 and 5 mm as the adult round to pear-shaped yeast What the 0 4 μ, 0 3 μ and 0 2 μ forms can be is only speculation, but some of these small forms other than coal or iron particles appear also to be part of the yeast cycle This theoretical concept fits the facts better than any other we have found To suggest that the parasites come from without would be untenable because the mass is strictly avascular The only thing left is to assume that some remain as resting residues (perhaps endospores) of active parasites of an earlier and active process Some normal sized parasites may have persisted but the small microspores are still unaccounted for

A most interesting feature was that the calcium stain (Von Kossa) reveals a remarkable pattern in the whole central area consisting of polygonal shaped patches that correspond to the original alveoli The borders are made up of calcium-impregnated round bodies which might be due to a combination of the calcium with nucleic acid of the alveolar cell nuclei This would indicate that instead of beginning as a small focus and building outward, the original focus was probably an infiltrate involving many alveoli After the building up of the capsule the enlargement progressed the same

The third group, or nodular type, ranges from a soft grayish mass that may vary from a millimeter or two up to 1½ cm in diameter or to dense encapsulated and calcified and even ossified lesions The soft lesion generally has more of a bluish-gray appearance than a tubercle of similar size, but this is not a sharp differentiation The microscopic appearance resembles very much that of a caseous tubercle with a central area of debris surrounded by a hyalinized band of caseated fibrous tissue outside of which may be varying amounts of granulation tissue Sometimes the lesions may be multiple as shown first by Christie and Peterson [17] The central area of

FIG 13

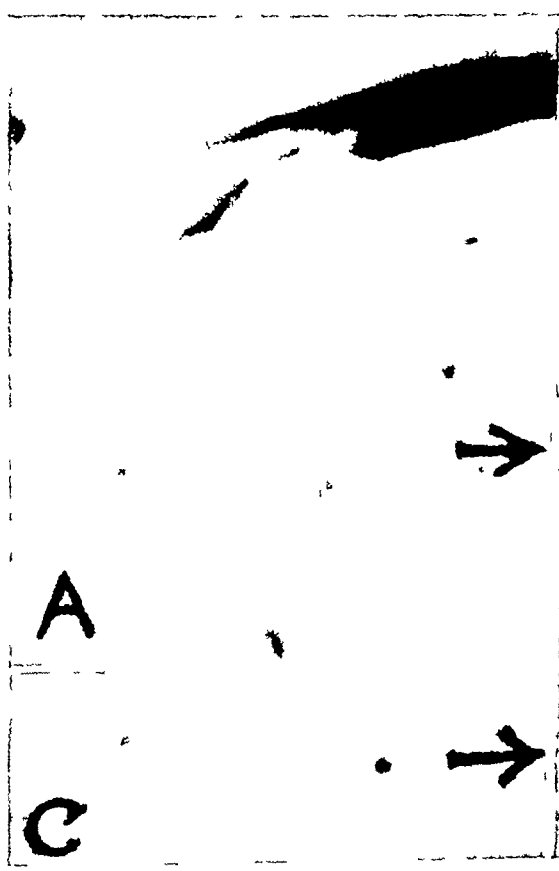


FIG 14

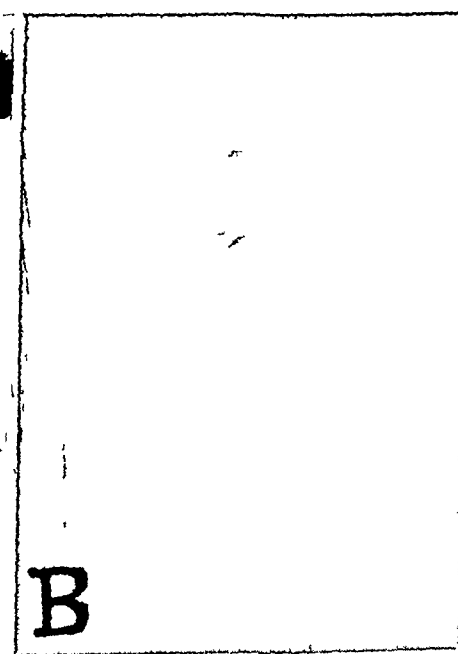


FIG 15

FIG 16

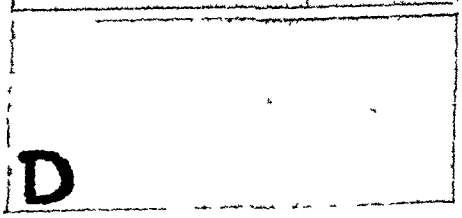


Figure 13 (A) A zone marked by "c" in Fig 7 where there is still fibrous tissue The dark staining bodies are smaller and assume a round granular appearance Most show no birefringence, but one in upper left is typical G M S stain × 3400—*Figure 14* (B) Polariscopic view of Fig 13 Only 2 or 3 show a faint birefringence G M S stain × 3400—*Figure 15* (C) Still further out in the fibrous tissue G M S stain × 3400—*Figure 16* (D) Polariscopic view of Fig 15 Only one shows typical birefringence Others only show points of light They may be artefacts × 3400

these masses is usually less dense than that of a corresponding tubercle There is a complete absence of polymorphonuclear leukocytes, lymphocytes and plasma cells, but occasionally red blood corpuscles may seep into the central area from the granulation tissue outside the wall As pointed out by Binford[14] the capsule is commonly made up of a palisade-like arrange-

FIG 17

FIG 18

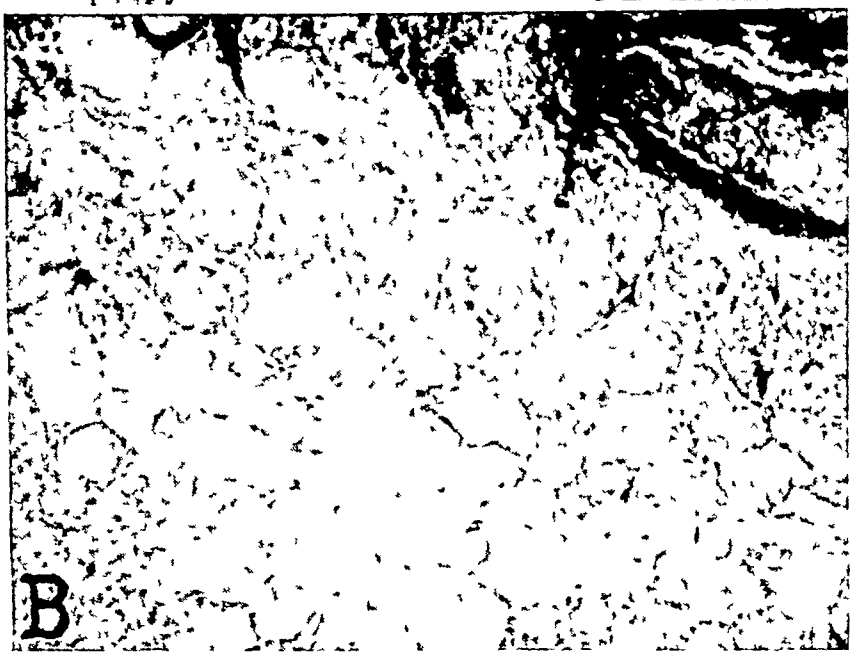


Figure 17 (A) A microphotograph of the central area of Fig 7 (the blood vessel marks the general location) Note the outlines of the alveoli caused by the calcium deposits in the alveolar wall, and possibly to a calcium salt of nucleic acid in the disintegrated nuclei of the alveolar walls × 48 Von Kossa stain —*Figure 18* (B) Another view similar to that of Fig 16

ment of cells pointing toward the center of the lesion As these lesions become larger, a central crevice appears that expands into a cavity Indentations may occur in the wall and a necrosis may extend far out into the tissue at one or several points around the periphery The fibrous tissue usually becomes hyalinized The central area is made of caseous debris, disintegrating red cells and macrophages, but no polymorphs or lymphocytes There is generally a much thinner type of grayish necrotic pus than there is in caseous tubercles Some of the lesions may become densely encapsulated and go through the same evolution as that observed in tuberculosis The central area may become densely calcified and actually ossified, which represents lesions of more than a decade in age In practically all these lesions we have found large numbers of the suspicious bodies that are thought to be H capsulatum The significance of these lesions *with respect to later disease is not determinable from the data at hand* It is thought possible that in the older lesions, especially the ossified ones several decades old, the parasites are dead The reason is that in some of the lesions no budding forms were found and some had lost birefringence almost entirely, but this is only speculation

Two illustrative cases will be given

D H B 21 No 25,139 (Fig 19A) This was a 45 year old Caldwell County farmer who recently was in St Luke's Hospital in Kansas City for diarrhea, fever, cough, fatigue, loss of weight which had taken place over a three month period An x-ray film revealed an infiltrate in the right apex with a diagnosis of probable tuberculosis He was advised to enter the Missouri State Sanatorium

His past history revealed that he had appendectomy in 1935, tonsillectomy in 1937, and stomach resection for ulcer in 1949 Laboratory examination revealed one skin test weakly positive for histoplasmosis Many were negative There was one weakly positive complement fixation test for histoplasmosis with several negatives *The tuberculin*

FIGURE 19 FIGURE 20

Figure 19 (A) Roentgenogram of D H B21, No 25,139, taken on August 11, 1955, showing a fibroid and partly infiltrative lesion in right subapex —*Figure 20* (B) Roentgenogram of T P B23, No 25,223, taken on November 10, 1955 showing a more inflammatory type of lesion in the left subapex

test was entirely negative Several cultures of the sputum were positive for H capsulatum as well as positive on mouse inoculation A culture of the lung tissue was also positive for H capsulatum

On December 13, 1955, right upper lobectomy was performed by Dr Polk and his assistants The pathological findings were as follows The specimen was that of the right upper lung lobe The lobe was of a reddish-black appearance on the surface with many black outlines of lymphatics On section, the appearance resembled somewhat that of a tuberculous process Several cavities and many masses of caseous material were seen The appearance resembled that of tuberculosis but the hue and arrangement of the caseation and the character of the caseation resembled that found in histoplasmosis The largest cavity in the subapical region measured about 2½ × 3 cms in diameter There were several bands across this cavity The cavity wall lining was slick and serous-like in appearance It was covered by adhesions that extended out into the parietal pleura and covered an area of several centimeters over the dome of the lobe The other cavities were smaller in size and did not have this bullous-like appearance They were found in the subapical region and extended well down toward the base of the upper lobe They ranged from 5 to 10 mm in diameter Most of them were multilocular The walls of these cavities were about 2 mm in thickness and had a dirty-gray granular appearance There was a sort of dirty-gray thin pus that was contained in these cavities which did not resemble the pus ordinarily found in a tuberculous process There were some infiltrative areas where the excavation of the cavity had not taken place All together there were probably 8 to 10 different areas of cavity formation or of infiltration from this disease process The lymph nodes did not reveal anything grossly The bronchi seemed to be normal

Microscopic examination of a number of sections revealed rather extensive chronic granulomatous involvement wherein there was seen much parenchymal replacement by varying sized lesions, some of which had a tubercle-like formation of fibrous elements and central multinucleated foreign body giant cell formation Others presented an occasional small central area of necrosis and around which there was pronounced fibrous proliferation and a chronic inflammatory reaction of a mixed type There were seen several irregular outlined lesions of caseonecrosis in which the lining elements were made up of compact fibrous tissue containing one to several multinucleated giant cells and relatively small numbers of reactive cells In some sections there were also seen pneumonic involvement wherein the alveoli were filled with macrophages, some of which contain hemosiderin pigment, others cellular debris In some of the giant cells there were seen asteroid structures, in others amorphous structures and occasionally some contained oval shaped, small, clear vacuole-like structures The lesions did not appear to be typical of tuberculous involvement Sections stained by the PAS stain revealed an occasional stained intracellular structure compatible with Histoplasma capsulatum The diagnosis was chronic granulomatous pneumonitis with cavitation secondary to Histoplasma capsulatum The supplementary report revealed that the G M S stain identified many lavender stained bodies that were 3-5 microns in size and were compatible with H capsulatum Final diagnosis Pulmonary histoplasmosis

Comment It is highly probable that three or four of the old calcific lesions were part of an old "primary complex," as Straub and Schwarz[17] have reported, but since we were not able to examine all of the lymph nodes it was not possible to prove this suspicion Several cases of definite primary complex of only a few years' duration will be reported later

In the more caseous lesions, even though they are well encapsulated, it is thought that most of the parasites are living, largely because of budding forms present In fact, some evidence seems to point to the fact that they survive as long or much longer than do tubercle bacilli in a similar type of lesion Thus the carrier state may be prolonged indefinitely, even if only a few infections ever develop into clinically active disease The yeast bodies are found in great abundance in caseation in contradistinction to tubercle bacilli

Some of these lesions may be similar in nature to the large encapsulated circumscribed lesions, except that the defensive balance operated sooner and produced a heavy impervious capsule that kept the lesion small and the parasites within bounds

The fourth group of cases consists of chronic pneumonitis These have been fairly well described by Binford and others, and it would appear that the development of these lesions is rather constant Probably it would be well first to describe the appearance of these lesions from the standpoint of gross pathology The condition existed in at least five of the cases that we studied and the pneumonitis extended into the fairly normal lung tissue beneath the cavity usually from 2 to 3 cm The appearance and the feel of the lesion grossly was similar to a tuberculous caseous pneumonia Microscopically, however, there was a considerable difference between this and an acute tuberculous lesion Finding this type of lesion in a patient that has been treated for a long time with anti-tuberculosis drugs is strong evidence in favor of histoplasmosis There was considerable variation in the pattern, but most of the lesion is granulomatous with epithelioid cell proliferation and varying numbers of Langhan's giant cells (Figs 23 and 24) There may also be areas of early organizing subacute fibrinous pneumonia with varying numbers of histiocytes present Then around the margins may be purely histiocytic infiltration, some of which may contain

FIG 21

FIG 23

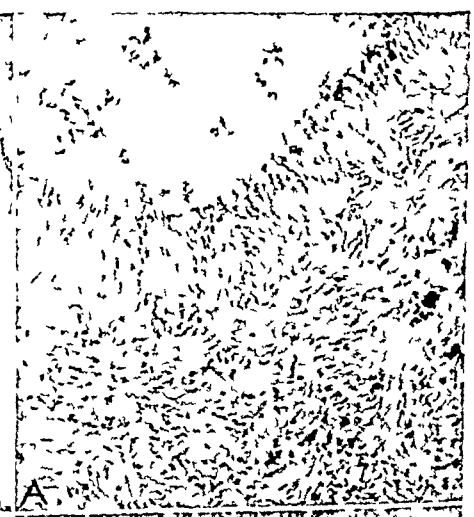


FIG 22

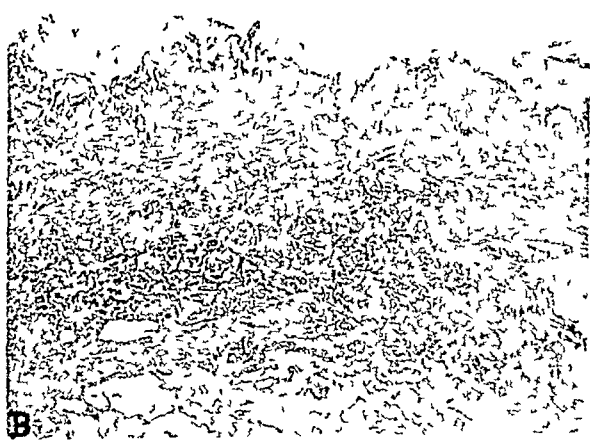


FIG 24

Figure 21 (A) A low power view of two of the fibroid cavities shown in Fig 17 H & E × 6—*Figure 22* (B) A higher magnification of wall of cavity marked off in Fig 19 H & E × 36—*Figure 23* (A) A still higher magnification of wall of cavity of Fig 19 Note palisade arrangement of cells H & E × 160—*Figure 24* (B) An area of chronic pneumonia in lung tissue showing alveoli packed with organizing fibrous exudate, with alveolar cells and macrophages H & E × 132

parasites, but as a rule the parasites were very rare in the granulomatous parts of the lesion

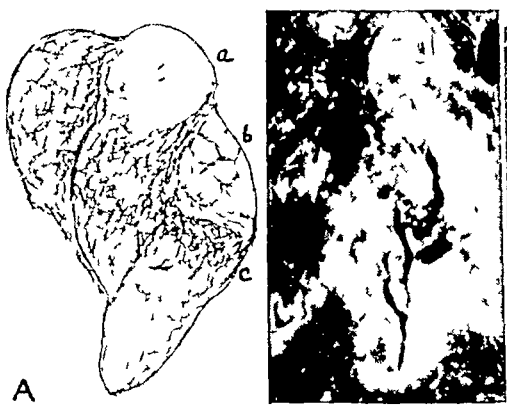
T P B 23, No 25,223 (x-ray shown in Fig 19B), was a 49 year old Ozark County farmer who had for 12 months complained of malaise, weakness and inability to cope with his duties A Mobile Unit found the lesion in the upper lobe of the left lung and he was sent to this hospital

The skin test was found strongly positive for histoplasmosis and negative for tuberculosis Complement fixation for histoplasmosis was negative One sputum specimen was positive on culture and produced disease in a mouse as reported by Dr Furcolow All other tests were negative including culture of lung tissue and lymph nodes Since the lesion was isolated in the left upper lobe the conference decided upon excisional surgery because of the possibility of cancer

On November 15, 1955, therefore, Dr Polk and his assistants did a lobectomy of the left upper and an excision of hilar nodes (Figs 25, 26 and 27)

Pathological findings of the upper lobe of the left lung and hilar nodes Gross The disease was rather extensive but there was much good lung tissue remaining, especially in the lingula and in the middle portion In the apex there was a great deal of caseous material and there were two or three small cavities, one of which measured 2½ cm in diameter with grayish, rather caseous walls, 2 to 3 mm in thickness There were two or three areas of what appeared like caseous pneumonia adjacent to these cavities In this pneumonic area were several soft, rather dry caseous "tubercles" measuring 2 to 5 mm in diameter There were two to three cavities that measured 1 to 2 cm in the midportion of the lobe The only abnormal feature in the lingula was that it

FIGURE 25 FIGURE 26 FIGURE 28



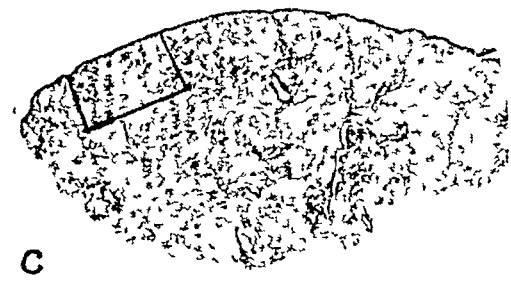


FIGURE 27 FIGURE 29

Figure 25 (A) A sketch of resected upper lobe of T P B23, No 25,223, purporting to show the cystic protrusion at "a," the chronic pneumonia at "b," and the atelectasis at "c"—*Figure 26* (B) A slightly enlarged caseous focus from the consolidated region below the cystic cavity with early cavity formation H & E × 45—*Figure 27* (C) A low power photo of section of the chronic pneumonitis at "b" in Fig 23 H & E × 45—*Figure 28* (A) A higher magnification of area marked off in Fig 25 H & E × 20—*Figure 29* (B) A still higher magnification of an area of the chronic pneumonitis Note the imperfect giant cells, fibroblasts, fibrosis, macrophages, and the few lymphocytes with no polymorphs H & E × 140

had much hypostatic congestion The lymph nodes near the hilum were not particularly enlarged and contained black pigment The bronchi were practically normal

Microscopic examination showed a chronic granulomatous inflammatory reaction characterized by presence of areas of caseonecrosis as well as areas of cavity formation and also small areas of pneumonic inflammatory reaction The cavitations and the areas of caseonecrosis were bordered by fibroblasts arranged more or less in a picket-fence formation with an occasional mononucleated cell of irregular outline Adjacent and also in other more distant areas there was a pneumonic involvement wherein the alveoli were filled with numerous histiocytes mostly of fibroblastic type Occasionally these showed an early central caseation A few of the giant cells contained asteroid-like structures and examination under high power and oil immersion showed the presence of only one small rounded intracellular structure which resembled a yeast body Preliminary diagnosis was histoplasmosis

A re-examination of the slides stained by PAS stain revealed many phagocytic monocytes that contained bodies appearing like Histoplasma capsulatum The G M S stain revealed many typical yeast-like bodies, some in the cavity walls showing budding, as well as a great many in the encapsulated areas These were of the same size and character of Histoplasma capsulatum Final diagnosis—Histoplasmosis

The fifth group, the ulcerative type, may be divided into the caseo-ulcerative and fibroid The former were cavities developing in caseous areas similar in most respects to the caseous nodular lesion, except that they were larger and it resulted in a central cavity which communicated with a bronchus (See Fig 26) Parasites may be found in the walls of most of these lesions, but they were not as numerous as they were in the encapsulated lesions In the other type of ulcerative lesion, the fibroid type, the cavity may be of a cystic nature with a relatively smooth wall and a thin fibrous cyst-like bulla that extends above the surface of the lung Another form was found to have a thin wall as a result of a rapid destruction of lung tissue similar to that of a progressive tuberculosis Again there were cases

FIGURE 30 FIGURE 31

Figure 30 (A) Roentgenogram of H T, B28, No 26,098, taken on September 16, 1949 showing a fibroid apical lesion in the left apex and a few nodules below It was called a moderately advanced tuberculosis with an apical cavity—*Figure 31* (B) Same case taken on August 31, 1956 showing what was thought to be a pneumothorax because of the fibrin body showing Instead it was found to be a completely destroyed lung

where there was a dense fibroid wall as much as two centimeters in thickness, simulating chronic fibroid tuberculosis In practically all but the recent ulcerative lesions, parasites were rather scarce in the cavity walls and difficult to culture, but were found in great numbers in the adjacent encapsulated lesions, either in the pulmonary tissue or in the lymph nodes An illustration of a progressive ulcerative lesion is afforded by the next case

FIG 32

FIG 33

FIG 34

FIG 35

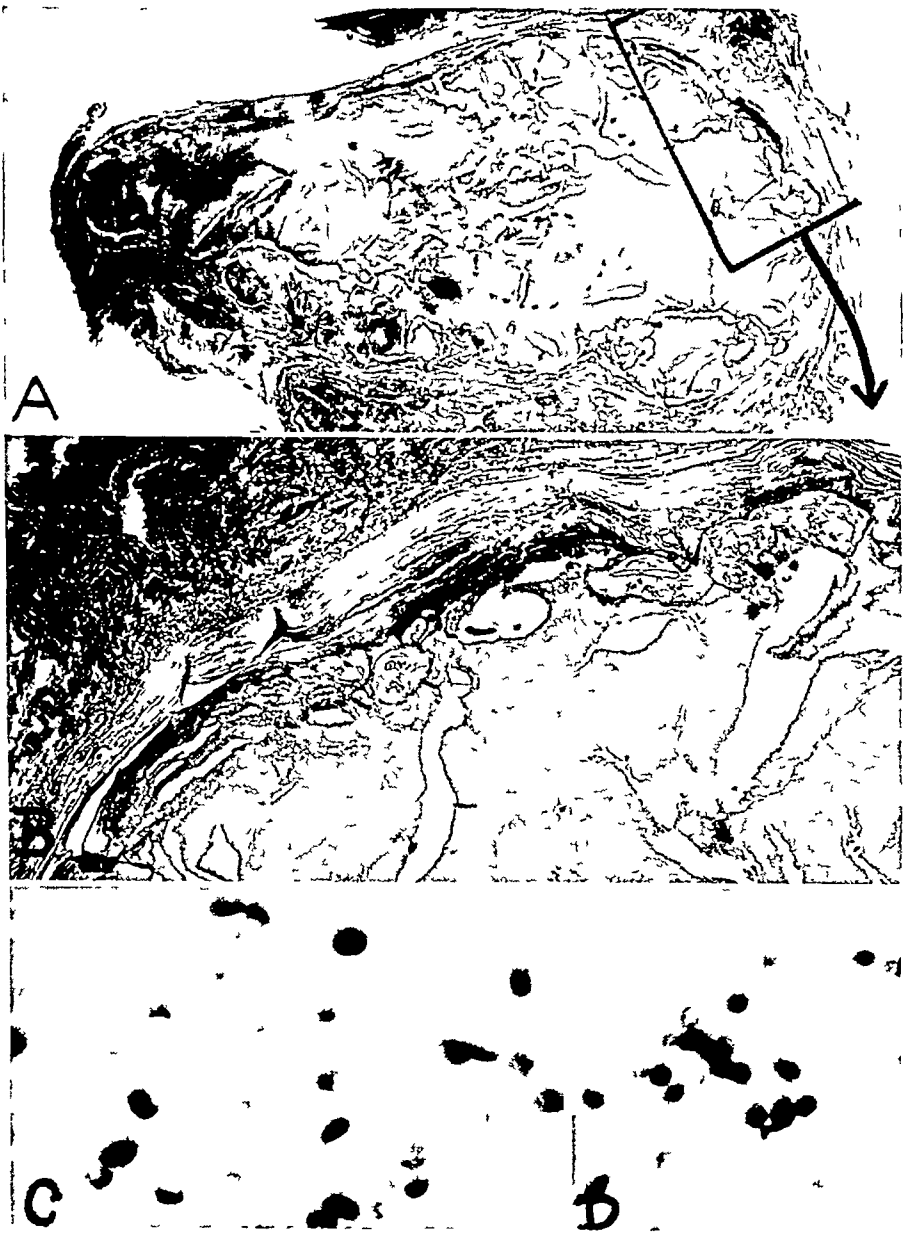


Figure 32 (A) A low power view of dense ossified parenchymal lesion shown in Fig 31 There was also a lymph node lesion left behind, perhaps the lymph node component of an old primary Small dots encircle several areas in which yeast bodies were found H & E × 45—*Figure 33* (B) An enlarged area outlined in black ink Note the bone and marrow—*Figure 34* (C) Microscopic view of yeast bodies found in area outlined by dots in Fig 32 G M S stain × 3200—*Figure 35* (D) Another field outlined by the dots in Fig 32 G M S stain × 3200

H T B 28, No 26,098 This was a 55 year old widowed Mississippi County laborer He gave a history of having a 12 year coal mining experience in Kentucky 25 years ago Since then he has worked in timber and saw-milling

In the past 20 years he had three bouts of "pneumonia" and several gastro-intestinal attacks thought to be due to gall stones and for which he was operated on in 1935 More recently he had severe chest pains with productive cough, loss of weight, chills, nightsweats, streaked sputum and bouts of fever An x-ray film showed a spot on the left upper lung field By 1947 he had a large hemorrhage which confined him to bed for six weeks Tubercle bacilli were never found An x-ray film in 1949 was read as "moderately advanced tuberculosis with a well defined cavity" Again on January 14, 1950 "Right negative except for calcifications in the hilum Left Diffuse haziness in the apex with ill defined mottling in the second interspace" This was after the patient had been admitted to our hospital on January 13, 1950 He was discharged May 5, 1950 as an arrested case

As a checkup an x-ray film taken August 11, 1953 was reported as follows "Right no change Left The areas of rarefaction in the upper lobe of the left lung were larger and so were the emphysematous blebs seen in the lower lobe" On March 19, 1955 "Right remains clear Left Has been completely destroyed since the previous film The entire upper third was occupied by a giant bleb or cyst and multiple large cysts occupy the remainder of the lung field"

On July 13, 1956 he was re-admitted to the hospital and the x-ray film reading was reported as follows "The left lung was thought to be collapsed with effusion and empyema In the right apex there was an area of rarefaction considered to be a small cavity" He had "heart trouble" with edema of the extremities He was treated with digitalis for the heart trouble and was unable to work since then He was advised to re-enter the sanatorium but refused, gradually becoming worse until he became bedfast He developed pain in the chest with continuation of the symptoms and had two rather large hemorrhages over the last two years before the second admission on July 13, 1956

The laboratory examinations have been uniformly negative for acid fast bacilli although there was abundant sputum and there were a large number of examinations One sputum culture was positive in our laboratory for H capsulatum Three successive gastric lavages were also positive for H capsulatum as was one fluid from the chest cavity All subsequent examinations for H capsulatum were negative or the cultures were over-grown with bacteria and Geotrichum The complement fixation test throughout this patient's second stay in the hospital was rather strongly positive, going as high as 1 64 dilution The tuberculin skin test was weakly positive There were no other positive findings, including the subsequent examination of the resected specimen for yeast by both Dr Furcolow and our own laboratory

After due consideration in the Staff Conference pneumonectomy was decided upon and was carried out by Dr Polk and his assistants on September 19, 1956 The pathologic findings were as follows The gross specimen representing the whole left lung was made up of an extensive cavity that involved the greater part of the organ The over-all dimensions of this specimen, including the decortication of the pleura, was about 20 cms from apex to base and about 15 cm wide and 10 cm in the third dimension It was difficult to estimate the dimensions of the cavity but it was a centimeter or two less each way than that given for the over-all measurements There were numerous blood vessels that crossed the cavity from the apex all the way to the base On dissecting down the larger bronchi, over half of them were found to terminate in this huge cavity The average bronchus was about 4-5 mm in diameter when it entered the cavity and there was a smooth opening of the bronchus at the point of entry This opening was rather flaccid and tended to make a valve-like structure in the cavity and helped to keep it distended Around the trunks of the main bronchi were areas of solid black atelectatic lung tissue

Microscopic examination showed very extensive alteration of the normal pulmonary tissue by chronic inflammatory process in which there was much fibrous proliferation with replacement of pulmonary tissue In areas bordering the grossly described cavitation, portions presented granulation tissue formation overlying an area of hyalin-like material More peripherally there was fibrous proliferation with secondary hyalin changes A portion of the cavitation presented a proliferation of the bronchial epithelial mucosa and occasionally this presented a metaplasia into the squamous cell type of epithelial membrane In one section there was an exudative lesion in which there were some neutrophils and mononuclear macrophages many of which contained ingested cellular debris and in a few there were seen intracellular inclusion structures which are round and had a capsular halo around them PAS stained tissue showed within this lesion several stained round structures with a clear halo around them which morphologically were compatible and certainly very suggestive of Histoplasma capsulatum A section of several lymph nodes showed the architecture to be essentially

intact The lymphoid follicles presented active normal centers In one there were a number of histiocytes containing anthracotic pigment No granulomatous inflammatory lesions were seen Diagnosis Left pneumonectomy showing chronic granulomatous pneumonitis with giant cavitation due to Histoplasma capsulatum

After a stormy postoperative period he expired September 29, 1956 All organs, both gross and microscopic, were not greatly abnormal Only the anatomic diagnosis will be needed for the purpose

(1) Missing left lung—status postpneumonectomy
(2) Chronic granulomatous inflammation of right lung, probably histoplasmosis, although no parasites were found
(3) Atelectasis of right middle and lower lobes

As with the other specimens, a re-examination of the material of this case was performed and a search for encapsulated and calcified lesions was made by very carefully sectioning every part of the lung specimens The oldest calcified lesions were heavily encapsulated with fibrous and ossified tissue and there were many erosions around the border and some extended into the centers of the lesion The open spaces left were filled with bone marrow surrounded by thin marginal strips of bone

The G M S stain revealed a large number of yeast bodies in several pockets within the calcified center (see Figs 32-35 incl) There were several accumulations of very small spore-like bodies in some places that appeared to be the beginning of the evolution of yeast bodies Some of the larger spore-like bodies were birefringent The smaller ones, less than one micron in diameter, only showed as a bright to orange point of light

A few parasites were found in the wall of the cavity but they would have been missed had not the others been found in the calcified lesions

Final diagnosis Fibro-calcareous and ulcerative histoplasmosis

Part II of this paper will appear in the September issue of
Diseases of the Chest

The Place of Steroids in Pulmonary Disease*

HARRY SHUBIN, M D, F C C P, ROBERT LAMBERT, M D, F C C P, CHARLES A HEIKEN, M D, F C C P and SAN SINGHAPHAKDI, M D

Philadelphia, Pennsylvania

This presentation will confine itself to the use of the steroids and their relationships, bad and good, to tuberculosis

Although the clinical significance of the adrenal glands was first reported by Addison in 1855, comparatively little was known of its physiology until Selye showed its relationship to the "stress mechanism" Further studies by Hench, et, al, proved clinically the relationship of cortisone in inflammatory and allergic reactions

Even at present, the corticosteroid preparations are clearly labeled as being contra-indicated in patients with active tuberculosis This is due to the adverse affects first noted in early animal experiments[1-3] and in humans in whom cortisone caused an exacerbation of a previously unknown or quiescent tuberculosis

Reports in the literature recently by various investigators[4-9] tend to show that the corticosteroids can be given safely with occasional dramatic results in active tuberculosis as long as anti-tuberculous therapy is being simultaneously administered This is especially true in fulminating tuberculosis such as miliary and tuberculous meningitis

This paper, therefore, will seem paradoxical, for it will tend to condemn a treatment where it has been previously advocated and advocate a treatment where it has previously been condemned

Following the excellent results obtained in the treatment of rheumatoid arthritis,[10] bronchial asthma, inflammatory and allergic dermatitis, and eye conditions, its use has expanded to rheumatic fever, nephrosis, lupus erythematosis and other collagen diseases, blood dyscrasias, etc

The first portion of this presentation will discuss cases of reactivated tuberculosis seen by the authors in patients receiving the corticosteroids for a variety of conditions The reasons for reactivation and possible methods of prevention will also be discussed

The second portion will review the results obtained by the use of steroids in patients with acute and chronic tuberculosis, who also were receiving antituberculous therapy

While it may be true that the number of reactivated tuberculosis cases is comparatively small in proportion to the general usage of the steroids, nevertheless they are being seen with increased frequency by chest specialists[11] and warrant a flag of caution to our colleagues in other fields of medicine Chart 1

The following cases illustrate typical reactivation

---

*Philadelphia General Hospital, Northern Division, and Rush Hospital

CHART 1

ACTIVE TUBERCULOSIS BY DISEASE TREATED WITH STEROIDS*

Total Patients	38
Rheumatoid Arthritis	11
Bronchial Asthma	10
Boeck's Sarcoid	5
Periarteritis Nodosa	1
Lupus Erithematosis	3
Dermatitis—Allergic	4
Addison's Disease	1
Ocular Diseases (Uveitis etc)	2
Polycythemia Vera	1

*Not one case covered by antituberculosis drugs

D K—This 33 year old, white, nurse was first seen in 1950 with lesions in the left hilar region and right mid-lung field During the next three years, this bilateral granulomatous type lesion gradually progressed to involve both mid-lung fields She was completely studied at the University of Pennsylvania and bacteriological studies were negative The tuberculin test, however, was positive She continued to work until 1953, when she went to a hosp tal in Texas While there, her condition was diagnosed as sarcoidosis and cortisone was administered

At the end of one month, she returned to Philadelphia and because of productive cough and fever, she was readmitted for check-up X-ray film revealed giant cavity in the right mid-lung field Sputum at this time was positive for tubercle bacilli

She is still being treated for tuberculosis but is now on an out-patient basis after three years in the hospital (Figure 1)

R H—40 years, colored, man Had his first x-ray film taken in April 1955 which revealed large thin-walled bullae in both upper lobes with fibrosis extending from the hilum in both mid-lung fields Tuberculin tests negative on all strengths, repeated sputum negative for acid fast bacilli Scalene node biopsy was reported positive for sarcoidosis He was placed on cortisone for one month without antituberculous coverage

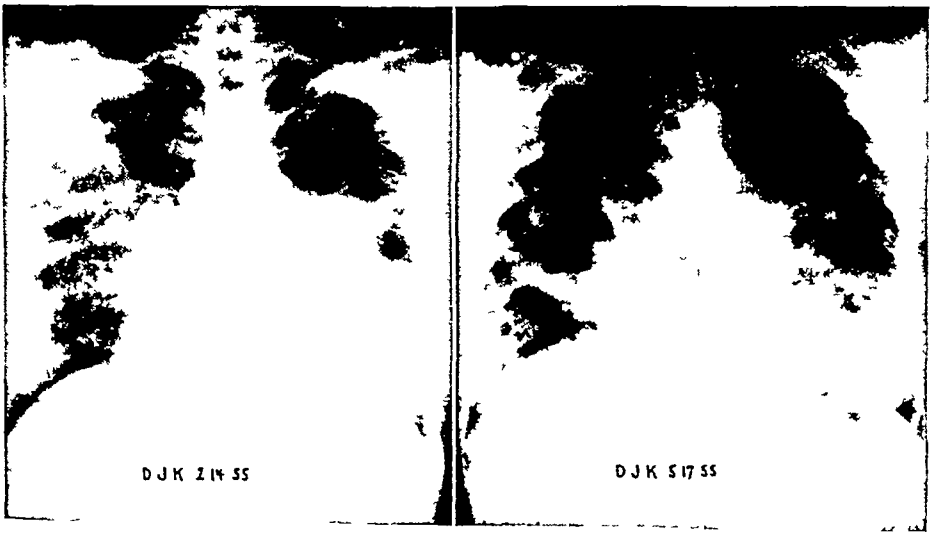


FIGURE 1

Two months later, while working at a steel mill, he had hemoptysis and was hospitalized where x-ray films revealed exudative type infiltration involving both lower lung fields Sputum at this time was highly positive for tubercle bacilli

He was then sent to Rush Hospital and started on streptomycin and INH He has improved on this regime, although moderate cor pulmonae has developed While the etiology of sarcoid has not been definitely proved, we feel these patients should not have steroid therapy without antituberculous drugs (Figure 2)

S P—59 years, white, man, was admitted to Temple University Hospital in July 1954 His past history revealed disseminated lupus erythematosis for one year, during which he received 100 mgm cortisone daily On admission, he was semi-stuporous, had left hemi paresis, and x-ray films showed far advanced exudative pulmonary disease Tubercle bacilli were found in his sputum He received streptomycin, INH and PAS, cortisone was discontinued and ACTH 20 U daily was given for two months He was transferred to Eagleville and Potassium Paba was started in September 1954, after stopping the ACTH, but continuing INH and streptomycin This regime is still being continued and he has had no recurrence of lupus with apparently stable inactive tuberculosis, after being at home for one year (Figure 3)

L H—This 63 year old, colored, man, was admitted to Rush Hospital February 10, 1956 for evaluation of lesion of chest He had been treated in the arthritis clinic of another hospital since June 1955 During this time he lost weight and developed cough He had been well until June 1955 when he developed arthritis of middle finger of left hand followed by swelling of hand and wrist Shortly thereafter, his knees became swollen and tender

Chest x-ray films on February 16, 1956 showed moderately advanced reactivated fibrocaseous pulmonary tuberculosis of the right upper lobe X-ray film of knees showed evidence of rheumatoid arthritis of right and left knee joints His erythrocyte sedimentation rate was 59 mm in 60 minutes Blood serology was reactive in Kolmer and VDRL Sputum positive for tubercle bacilli Aspirated fluid from the knee was negative on smear and culture for acid fast bacilli

Therapy was instituted with streptomycin and PAS and orthopedic care given to his knees Duracillin was given, 600,000 units daily, for 10 days for reactive serology He showed clinical improvement became afebrile, and slightly gained weight This indicates the danger of using steroids in arthritis without preliminary and follow-up chest x-ray films for pulmonary pathology (Figure 4)

W C—was admitted to Rush Hospital December 4, 1956 with a diagnosis of bronchial asthma and possible pulmonary tuberculosis Past history was positive for syphilis, for which he received treatment with the last serology report being negative a month prior to this admission Before being hospitalized at Rush, he was in another hospital for asthmatic attacks and had a history of 20 lb weight loss During that hospitalization he was told that he had pneumonia He developed indigestion and bloody stools but a gastrointestinal series was negative However, he improved on an ulcer regime While at Chester County Hospital, he had received cortisone for resistant asthma He was consistently negative for acid fast bacilli while at Chester County Hospital However, at Rush Hospital, sputum on smear was positive

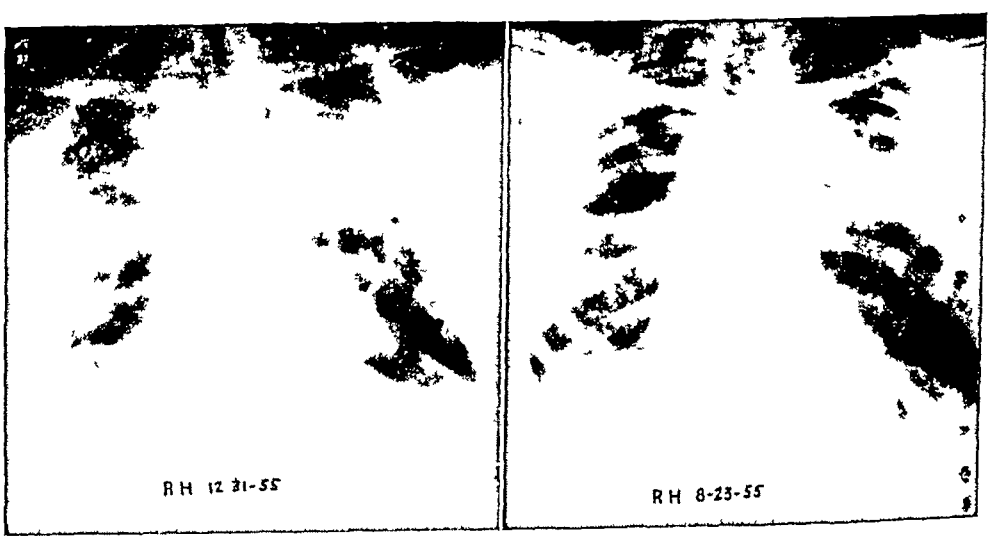


FIGURE 2

CHART 2A
THE USE OF STEROIDS IN TUBERCULOSIS WITH ANTITUBERCULOUS THERAPY

Acute Tuberculosis		33 Patients
Miliary	12	12 excellent
Meningeal	11	8 excellent 3 deceased (1 encephalitis; 1 within 72 hrs; 1 staph-pneumonia)
Pneumonic	8	7 excellent 1 deceased (within 24 hrs)
Lymphatic	2	2 excellent

on three occasions He was then placed on streptomycin and INH X-ray films of the chest revealed evidence of caseous pneumonic disease of the left upper lobe on December 5, 1956 The last film on February 8, 1957 showed improvement in the pulmonary tuberculosis with residual evidence of cavitation, with positive sputum

This patient illustrates two complications of steroid therapy, that is, the reactivation of pulmonary tuberculosis and exacerbation of gastric ulcer with possible gastrointestinal hemorrhage (Figure 5)

The main reasons for reactivated tuberculosis in this series were

1) Failure to investigate the possibility of latent or inactive tuberculosis

2) Failure to administer anti-tuberculous drugs with the steroids

3) Excessive dosage and prolonged administration It is easy to understand how complications develop from excessive dosage when we consider the amount of secretion of ACTH[12 13] from the anterior pituitary does not exceed one unit daily while the normal daily secretion of hydrocortisone from the adrenal cortex varies between 12 and 20 mgm in 24 hours

Most steroid therapy is given in doses far in excess of that normally produced or needed by the body and generally when administered for periods longer than 10 days may lead to hypercortonism and suppression of the adrenal glands

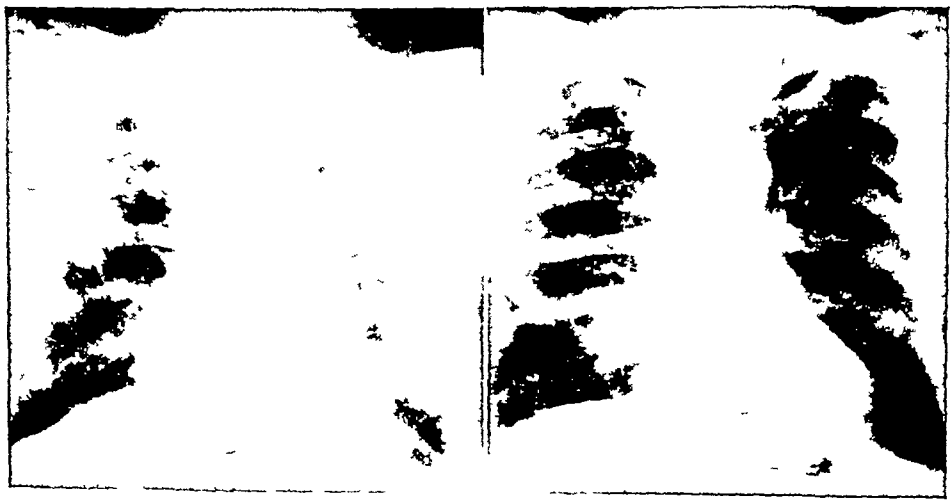


FIGURE 3

While the newer, more powerful analogues of cortisone—that is, (prednisone and prednisolone) are popular because of fewer side effects, they are equally as dangerous in producing complications of overdosage, especially since they are often administered in the presence of normally functioning adrenals

Even more alarming is the recent tendency to combine prednisone in doses of from 1 to 2 mgm with analgesics and antihistamines Although this amount might appear to be innocuous, two of these tablets taken in the recommended dosage four times daily is in excess of the normal daily requirement of the body This problem would be magnified if such compounds ever became available without prescription

As a result of these findings, it is recommended that the following basic principles be considered

1) Administer the minimal maintenance dose necessary to obtain desired clinical results

2) Tuberculin test and x-ray film of the chest of all patients before starting therapy

3) If suspicious of latent or inactive tuberculosis, administer simultaneous anti-tuberculous therapy

4) After steroid therapy is discontinued, the patient's reaction to stress is diminished for at least the next six months The readministrations of steroids at times of stress, such as surgery or infections, is not only necessary but life-saving

The interest of the authors in the simultaneous use of steroids and anti-tuberculous therapy in active tuberculosis was aroused in 1954 In spite of the many good results with chemotherapy in tuberculosis, there were still a group of patients who had received all forms of therapy without clinical or x-ray improvement The possibility of adrenal insufficiency as a factor in the poor response was considered, is confirmed

FIGURE 4

CHART 2B

Chronic Tuberculosis		60 Patients
Terminal type	11	8 survived 3 deceased (within one week)
Allergic drug reaction	14	7 successful 6 successful—with surgery 1 deceased (within 24 hours of surgery—"shock syndrome")
Active cases no longer responding to drugs	35	24 improved 11 unchanged

by the low 24 hour 17 Ketosteroid output Since it has been shown that infections such as tuberculosis produce acute stress early in fulminating lesions and chronic stress in the prolonged form of disease Resistance of the host to infection is dependent upon the reaction of the hypothalamus-pituitary-adrenal axis It is fortunate that most tuberculous patients with normally functioning adrenals adapt themselves well to this stress This study indicates that the steroids should be used in those patients whose adrenals have become exhausted and they do not react favorably to the stress of disease Therefore, the first studies were in patients with poor prognoses from acute miliary or meningeal tuberculosis As a result of the favorable response in the original terminal patients, the use of steroids was gradually expanded to include the more chronic forms of tuberculosis which were not responding to combined anti-tuberculous therapy, and to those showing allergic reactions to anti-tuberculosis drugs

Prednisolone (Steiane) was given to 33 acute and 60 chronic cases as shown on the chart "The Use of Steroids in Tuberculosis *With* Anti-tuberculous Drugs" Chart 2 The following cases are typical of results in acute forms of tuberculosis

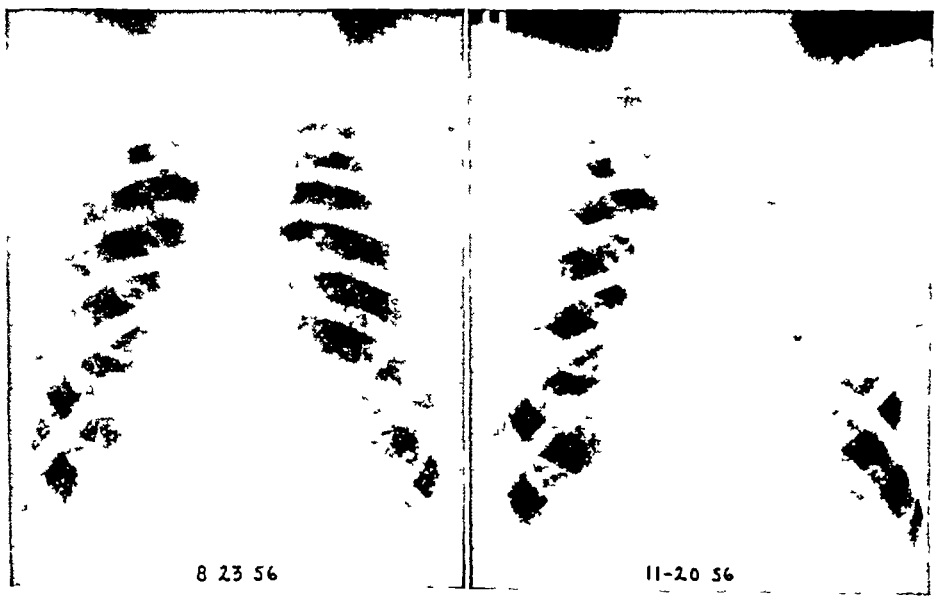


FIGURE 5

A M—This 41 year, colored, man, was admitted to Philadelphia General Hospital, Brockley Division, July 1954, toxic with left pleural effusion and x-ray film evidence of miliary tuberculosis He did not react to the second dose of PPD Streptomycin, INH and PAS, were administered but after two months, his clinical condition was worse, with temperature 103°F X-ray films showed spreading disease and he was practically moribund Pleural and urine cultures were reported positive for acid fast bacilli Cortisone was started, 200 mgm daily plus the three antituberculous drugs, and gradually reduced to 25 mgm daily in a month After one month, there was marked x-ray film clearing, he became afebrile and cortisone was discontinued He then noted to the first dose 2 PPD He remained in the hospital on triple drug therapy for six more months, when he was asymptomatic and the chest x-ray film appeared clear He has been followed as an out-patient, and still maintains good health

O B—This 15 year old, colored, boy was, admitted to Women's Medical College Hospital with cough, weight loss, fever and x-ray film evidence of miliary tuberculosis Although there was no symptom of meningeal irritation, a spinal tap was done It was negative for cells but showed slight increase in protein and decrease sugar Streptomycin, INH and PAS were started on the day of admission Meningeal irritation developed 36 hours after admission and repeat tap showed 275 cells, predominantly lymphocytes, increased protein and decrease sugar compared with previous tap Prednisolone, 60 mgm daily was started with prompt reduction in temperature Within three days all signs of meningeal irritation had disappeared The prednisolone was gradually reduced by 2 5 mgm a day and finally discontinued after five weeks Three weeks later x-ray film showed marked clearing of miliary infiltration

He continued to improve clinically and because of the marked clearing of the x-ray film, this case was considered by some doctors to have sarcoidosis instead of tuberculosis However, after three weeks, the culture from the spinal tap and sputum examinations revealed acid fast bacilli

He was followed for six months after cessation of therapy with prednisolone and discharged with apparently clear lungs, inactive disease and negative spinal fluid The triple anti-tuberculous therapy is being continued (Figure 6)

The following illustrate results in chronic forms of tuberculosis

M B, was admitted to Rush Hospital June 21, 1956, acutely ill Physical examination was difficult because of the condition Blood pressure 110/80 There were moist rales, bilaterally, anteriorly and posteriorly His temperature was 104° F on admission

Hemoglobin was 10 5 Gm, and there was a faint trace of albumen and occasional white cells in the urine Serology was non-reactive, fasting blood sugar was 80 mgm, BUN was 5 0 mgm and 17 Ketosteroids were 4 3 mgm in 24 hour urine specimen Sputum was positive and x-ray film revealed bilateral diffuse fibrotic and caseous pneumonic excavative process bilaterally, having the appearance of tuberculosis with

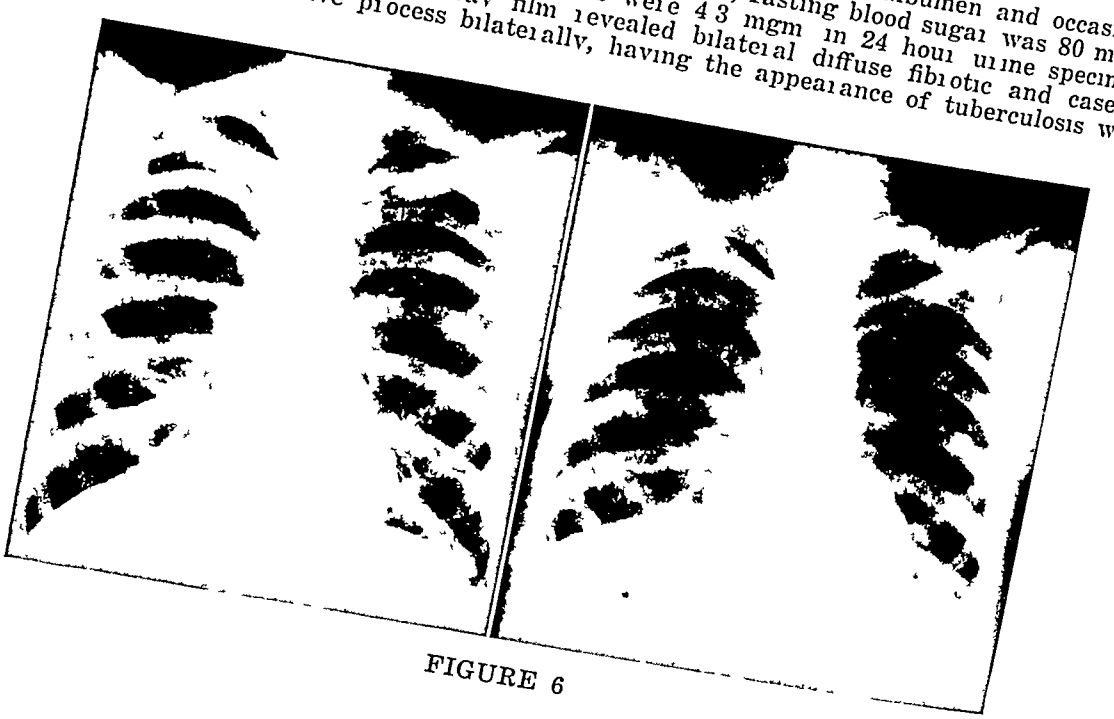


FIGURE 6

associated pneumoconiosis to be excluded He remained toxic, with temperature about 101° F

Chemotherapy was started June 23rd with distreptomycin and PAS On August 14th INH was added and the Steirane routine on September 25th He became afebrile by October fifth His cough had decreased and he had gained 23 lb since admission

X-ray film on October 31st showed marked improvement in the tuberculosis, which was apparently superimposed upon pneumoconiosis He is continuing treatment at Veterans Administration Hospital, East Orange, New Jersey (Figure 7)

J A D This 47 year old white man was admitted to Rush Hospital May 16, 1956 There was marked weight loss, fever and malnutrition, blood pressure 95/70 A diagnosis of far advanced pulmonary tuberculosis was made in addition to cirrhosis of the liver, peripheral neuritis and malnutrition He was overly alert, active and talking incoherently His sputum was positive for tubercle bacilli Fasting blood sugar 105 and BUN 4 7 mgm Hematocrit 25 per cent, 17 Ketosteroid 24 hour urine 3 3 mgm , urine showed trace of albumen, white blood cells two to four per high power field with occasional red blood cell, moderate number hyaline casts Hemoglobin 8 5 Gm , and Wassermann negative

Chest x-ray film on admission revealed far advanced bilateral fibrocaseous and caseous pneumonic pulmonary disease with multiple areas of cavitation An electrocardiogram showed some evidence of cardiac abnormality, probably electrolyte imbalance There was a petechial rash on his hands, wrist and face The liver was felt four fingers below costal cage and there was four plus pitting edema of feet

He was started on INH and streptomycin, high vitamin diet and sedatives He had two transfusions a few days after admission, receiving 500 cc of whole blood each time He was also started on the steroid routine In September, he began to develop epigastric pain and since it was felt there might be an ulcer, he was put on ulcer regime He began to improve clinically and gained weight to 130 lb Because of recurrent spiking of temperature, systemic infection was thought to be present Gall bladder films were negative By October, cortisone was slowly reduced and he received in addition, ACTH Blood pressure was now 120/78 and the sputum was negative by smear and culture Ketosteroids 3 1 mgm His urine was essentially normal X-ray films showed improvement but a major lesion was still demonstrated in the upper lobe of the left lung

The steroids apparently saved him from progressive, probably fatal condition, and now enables us to control his disease (Figure 8)

In exerting its anti-inflammatory effect, the steroids reduce toxicity and fever, appetite improves with weight gain, resulting in improved morale The reduction of toxicity is illustrated by the following case

W M S This 41 year old colored housewife was admitted to Philadelphia General Hospital, Northern Division, on July 10, 1956 with history of cough, productive sputum,

FIGURE 7

dyspnea and sweats for four months She also has chest pain, anorexia and weight loss from 115 to 86 pounds X-ray film showed extensive pulmonary lesions with large multiple areas of cavitation of the entire upper half of right lung She also had disease in the left lung Her sputum contained acid fast bacilli She received triple drug therapy for three months with slight improvement X-ray film showed no appreciable change, and she continued febrile

Streptomycin regimen was started on October 1, 1956 and her temperature returned to normal X-ray films on November 21 and December 31, 1956, February 1 and March 4, 1957, showed progressive improvement with marked clearing of the exudative shadows After three months of treatment, she gained from 80 to 114 pounds and had persistently negative sputum

The marked weight gain is shown by the next case

E D This 55 year old colored man was admitted to Philadelphia General Hospital Northern Division, on December 27, 1956 with far-advanced bilateral active pulmonary tuberculosis He was placed on Distrycin and PAS with poor results He lost from 124 to 113 pounds in less than two months and became worse clinically He raised more sputum which was consistently positive His x-ray film appearance remained essentially unchanged Streptomycin was started on February 9, 1957 and he gained to 140 pounds in two months Although there is still little change in the x-ray film appearance, his sputum has been negative since March 20, 1957 and he feels much better Because of this improvement, he can now be considered for other definite therapy

Discussion and Conclusions

Any major discovery in medicine is accompanied by complications or side-effects, until its proper place in our armamentarium is determined The steroids are no exception The original cortisone or hydrocortisone drugs produced electrolyte imbalance, sodium retention and subsequent fluid retention, etc, which is not seen with prednisone or prednisolone

However, its beneficial effect in rheumatoid arthritis, asthma, collagen diseases, etc, is counteracted by the reactivation of latent or inactive tuberculosis This has been observed in 38 patients of which five typical reactivations were discussed The patient must be studied for evidence of pulmonary tuberculosis and if doubtful, give anti-tuberculosis drugs Finally, use minimum dosage of steroids for short periods to obtain desired effects

FIGURE 8

The results on 93 patients in this study further proves the value of steroids in the treatment of tuberculosis Its effect may be life-saving in the acute, toxic forms, hastens desensitization and is beneficial in some patients with chronic tuberculosis It is always effective chemotherapy

What appeared a paradox in determining the place of steroids in pulmonary diseases, can now be properly evaluated by having complete studies of patient before and during treatment, and proper protective therapy against tuberculosis during steroid administration

SUMMARY

This presentation attempted to determine the place of steroids in pulmonary diseases, especially tuberculosis The beneficial effects of various steroids in rheumatoid arthritis, asthma, collagen diseases, etc, are well known However, we reported 38 patients, who had reactivation of latent or inactive tuberculosis following such therapy The physician must investigate the presence of tuberculosis, by skin test and x-ray films, and when in doubt, simultaneously administer anti-tuberculosis drugs Only by using these drugs judiciously, that is, the minimum dosage for the shortest period necessary to obtain the desired effects, are complications diminished

Paradoxically, the value of steroids in the treatment of tuberculosis has been established From its life-saving action in 33 acute, toxic, miliary, meningeal, etc, to its stimulation effect in 60 chronic patients, either prolonging their lives, or hastening desensitization thus allowing more effective therapy All of these patients received effective anti-tuberculosis chemotherapy during this study

---

Acknowledgment We wish to thank Doctors R V Cohen, L Collins, H Israel R Katzin, E W Marshall, R Mayock and J Schley for allowing us to use some of their patients in this study, and Doctors M Carlozzi and K Dumas of Chas Pfizer & Co for supplying the prednisolone and for their cooperation

RESUMEN

Esta comunicación intenta determinar el lugar que ocupan los esteroides en el tratamiento de las enfermedades pulmonares y en particular en tuberculosis Los benéficos efectos de los diversos esteroides en la artritis reumatoide, el asma, las enfermedades de la colágena, etc, son bien conocidos

Sin embargo, relatamos el caso de 38 enfermos que han tenido una reactivación de tuberculosis latente o inactiva después de tal terapéutica El médico debe investigar la presencia de tuberculosis por las reacciones cutáneas y las radiografías y en caso de duda administrar simultáneamente las drogas antituberculosas Sólo usando estas drogas juiciosamente, esto es, con la dosificación mínima por el más corto período de tiempo necesario para obtener los efectos deseados, disminuyen las complicaciones

Paradójicamente, el valor de los esteroides en el tratamiento de la tuberculosis se ha establecido

Sus efectos van desde el que hace al salvar la vida de 33 casos de formas agudas, tóxicas, miliares y meníngeas, hasta el estimulante en 60 casos crónicos ya sea prolongando sus vidas o acelerando la desensibilización permitiendo así una terapéutica más efectiva Todos estos enfermos recibieron quimioterapia antituberculosa efectiva durante este estudio

RESUME

Cette communication tente de déterminer la place des stéroïdes dans les affections pulmonaires, et particulièrement la tuberculose Les effets favorables des différents stéroïdes dans l'arthrite rhumatismale, l'asthme, les maladies du collagène, sont bien connus Cependant, les auteurs ont rapporté l'observation de 38 malades, pour qui un tel traitement entraina une réactivation de tuberculose latente ou inactive Le médecin devrait faire les investigations nécessaires pour reconnaitre la présence de tuberculose par tests cutanés et radiographies, et s'il y a un doute, administrer en même temps que le produit des médications antituberculeuses Par le seul emploi judicieux de ces médications, c'est-à-dire en utilisant le dosage minimum pendant la période de temps la plus courte pour obtenir les effets désirés, on diminue les complications

Paradoxalement, la valeur des stéroïdes dans le traitement de la tuberculose a été bien établie Elle va de l'action salvatrice dans 33 cas aigus, toxiques, miliaires ou méningés, etc à l'effet stimulateur chez 60 malades chroniques, soit en prolongeant leur vie, ou en hâtant la désensibilisation et par conséquent en permettant une théapeutique plus efficace Tous ces malades reçurent une chimiothérapie antituberculeuse effective pendant cette étude

ZUSAMMENFASSUNG

Diese Darstellung unternimmt den Versuch, den Platz der Steroide bei Lungenkrankheiten, besonders bei Tuberkulose zu bestimmen

Die Heilwirkungen verschiedener Steroide bei rheumatischer Arthritis, Asthma, Bindegewebserkrankungen usw sind wohl bekannt Wir berichteten jedoch über 38 Patienten, bei denen eine Reaktivierung einer latenten oder inaktiven Tuberkulose einer solchen Behandlung folgte Der Arzt muss auf das Vorliegen von Tuberkulose durch Hautproben und Rontgenaufnahmen untersuchen und in Zweifelsfallen gleichzeitig antituberkulose Mittel verordnen Nur durch vernunftigen Gebrauch dieser Mittel, d h die kleinste Dosis fur die kurzest notige Zeit zur Erlangung der gewunschten Effekte, setzt man die Komplikationen herab

Im entgegengesetzten Sinn wurde sodann der Wert der Steroide bei der Behandlung der Tuberkulose bestimmt Von ihrer lebensrettenden Wirkung bei 33 akuten, toxischen, miliaren, menigialen usw Patienten bis zu ihrer stimulierenden Wirkung bei 60 chronisch Kranken entweder hinsichtlich einer Lebensverlangerung oder einer Beschleunigung der Desensibilisierung wird so eine wirksamere Therapie moglich Alle diese Kranken erhielten eine wirksame antituberkulose Chemotherapie wahrend dieser Untersuchung.

REFERENCES

1 Lurie, M B, Zappasodi, P, Dannenberg, A M and Schwarz, J B "Constitutional Factors in Resistance to Infection The Effect of Cortisone on the Pathogens of Tuberculosis," *Science*, 113 234, 1951

2 Ebert, R H "In Vivo Observation on the Effect of Cortisone on Experimental Tuberculosis Using the Rabbit Ear Chamber Technic," *Am Rev Tuberc*, 65 64, 1952

3 Karlson, A G and Gainer, J H "Influence of Cortisone on Experimental Tuberculosis in Guinea Pigs," *Dis Chest*, 20 469, 1951

4 Chakravarty, S "The Place of ACTH and Cortisone in Therapy of Tuberculosis" In Antibiotics Annual 1955-1956, New York, *Medical Encyclopedia, Inc*, 1956, pp 192-201

5 Shubin, H and Heiken, C A "A Study of Effects of Steroids on Patients with Tuberculosis," Antibiotics Annual, 1956-1957, *Medical Encyclopedia, Inc*, New York 1957, pp 437-446

6 Houghton, L E "Combined Corticotrophic Therapy in Pulmonary Tuberculosis," *The Lancet*, — 595, 1954

7 Crofton, J Southfield Hospital, Liberton, Edinburgh Personal communication, October 1, 1956

8 Handley, A E "The Use of Corticosteroids in Combination with Isonicotinic Acid Hydrazide in the Treatment of Advanced Bilateral Progressive Cavitary Pulmonary Tuberculosis," *South African M J*, 30 605, 1956

9 Favez, G and Aguet, F "Hydrocortisone and Prednisone for Active Pulmonary Tuberculosis," *Schweiz med Wschr*, 86 843, 1956

10 Hollander, J L *Comroe's Arthritis and Allied Conditions*, ed 5, Philadelphia, Lea & Febiger, 1953, pp 319-336

11 Charpin, J and Beranger, J "The Risk of Tuberculosis in Adrenal Cortex Therapy," *Presse med*, 64 1507, 1956

12 Bethune, J E, Ganong, W F, Hume, D M and Nelson, D H "Plasma Levels of ACTH in Normal Subjects and Addisonian Patients Following Corticosteroid Administration," presented at meeting, Endocrine Soc, Chicago, Ill, June 7-9, 1956, abstracted, *J Clin Endocrinol*, 16 913, 1956

13 Kern, R *Am College Chest Physicians*, Post Graduate Course, Philadelphia, March, 1957

Lobarspirometry*

I. Description of the Catheter and the Technique of Intubation

E R CLARKE, JR, M D, C J MARTIN, M D and SERGEI POLITOFF
Seattle, Washington

Introduction

The ability to measure the function in anatomical divisions of the lung has not kept pace with the surgeon's competence in resecting smaller and smaller units Knowledge concerning the relative function of small divisions has been derived from pre- and postoperative bronchospirometric measurements, since techniques for direct measurement have not been available until recently [1]

In 1951, a spirometric catheter for the direct measurement of lobar function was designed in this laboratory The first model was tested in 1953, and was improved upon as a result of subsequent experience The purpose of this paper is to describe this catheter, to discuss the technique of intubation, and to indicate situations in which use of this catheter may be of particular value

The Catheter

The catheter (Fig 1A) is a three-lumen, soft latex-rubber tube 40 cm long and from 1 1 cm to 1 5 cm in outside diameter One channel extends the entire length of the catheter, and forms the airway to the lower lobe A second channel parallels the first until, near the tip of the catheter, it turns away at 90° and forms the airway to the upper lobe Each of the airways to the upper and lower lobes has an internal diameter of approximately 5 3 mm The third channel, considerably shorter than the other two, is the airway to the contralateral lung, and has an internal diameter of approximately 6 5 mm

The most distal balloon, when inflated, occludes the main stem and upper lobe bronchus, thereby functionally separating the lower and the upper lobe The detail of this balloon is shown in Figure 1B The proximal balloon occludes the trachea, and acting together with the distal balloon, isolates the contralateral lung

Figure 1C illustrates the body of the catheter in cross-sectional diameter, and shows the relationship of the five lumina to one another and the means of assuring only minimal wastage of space At the lower and upper ends of the catheter these triangular divisions become rounded, and continue as a tube

At the tips of the upper- and lower-lobe channels, two parallel lead-foil strips are embedded in the rubber to provide fluoroscopic identifica-

From the Cardiopulmonary Laboratory, Firland Sanatorium and the Department of Medicine, University of Washington
Supported in part by research grants G3380 and H1892 from the National Institutes of Health, U S Public Health Service
Presented before the Interim Session, American College of Chest Physicians, Seattle, Washington, November, 1956

tion of the channels during intubation Since the left main bronchus is considerably longer than the right, it is seldom feasible to use the same catheter for studies on both sides, and we have therefore built right- and left-handed models In the right lung, anatomical considerations require that the middle lobe be measured with the lower lobe

Intubation

With pre-medication and under topical anesthesia, intubation is carried out as for routine bronchospirometry A spring-steel, wire guide is inserted into the lower lobe channel, and bent to the proper angle to guide the catheter into the trachea The configuration of the upper lobe channel at the distal end of the catheter may make introduction of the tip through the glottis troublesome This aspect of intubation may be simplified by bending the laterally projecting, upper-lobe channel parallel with the lower-lobe channel, and then exhausting the residual air in the distal balloon The vacuum in this balloon holds the two channels parallel until they have entered the trachea The wire guide is then removed

Under fluoroscopic control, the catheter is then placed in the appropriate main stem bronchus The vacuum in the distal balloon is released and the catheter is rotated and moved up and down until the upper lobe channel suddenly moves laterally and engages in the upper lobe bronchial orifice The distal balloon is then inflated until traction on the catheter meets with resistance, and does not dislodge the channel from its position within the upper lobe bronchial orifice Care must be taken not to inflate this balloon more than is necessary to stop leakage, since with

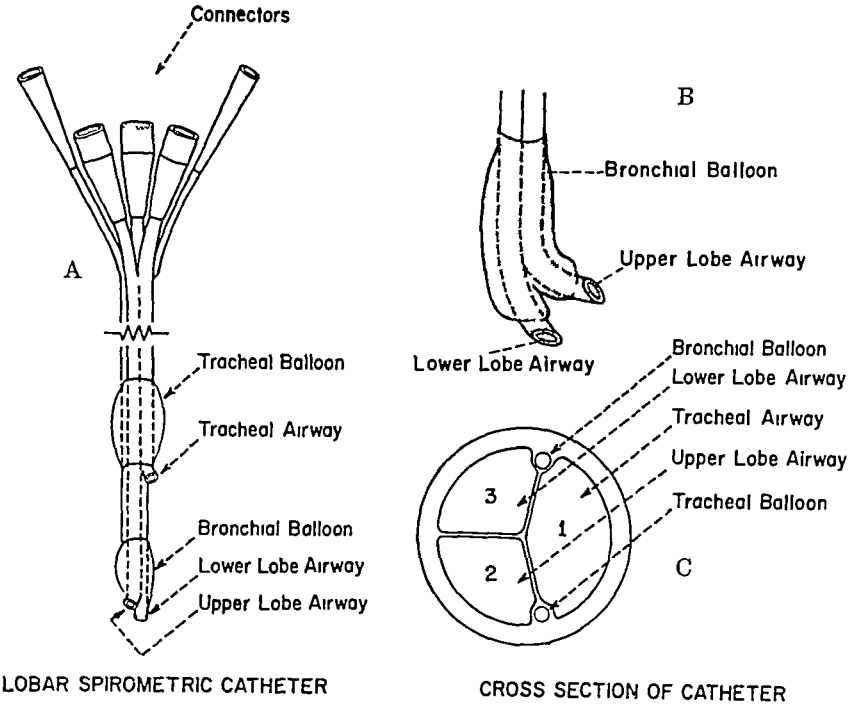


FIGURE 1 Lobarspirometry catheter, arrangement of the three airways and isolation balloons is shown in A, the detail of the tip in B, and the cross section in C

over-inflation, the carina may be pushed aside and compromise the bronchus to the contralateral lung

When the catheter is firmly in place, the subject lies supine, and recording spirometers are attached to each of the three airways The proximal balloon is inflated, and simultaneous recordings are made from the upper lobe, the lower lobe, and the contralateral lung If the functional isolation of each unit is complete, no spirometer will record a loss of volume Weighting of one spirometer bell will not cause either of the others to rise if the seal in the balloons is adequate A vital capacity maneuver must not reveal any obstruction As an additional check, we have routinely used the nitrogen meter to sample one unit while 100 per cent oxygen is ventilating the others When the check for the adequacy of the functional isolation is complete, the usual recordings of oxygen uptake and ventilation may be made

To determine the flow characteristics of the lobar spirometric and two commonly used bronchospirometric catheters (Zavod and Carlens), an E Greiner flow meter was mounted in series with the catheters The connector had a lateral arm leading to a water manometer The catheters selected for testing had similar outside diameters (14mm) The resistance to air flow through the combined upper- and lower-lobe lumina of the lobar catheter is almost identical to that in the left lumen of the Carlens bronchospirometric catheter (Fig 2) The flow resistance in the Zavod catheter is markedly greater than those in the other two Individually determined, the flow resistances of the upper- and lower-lobe lumina are almost equal

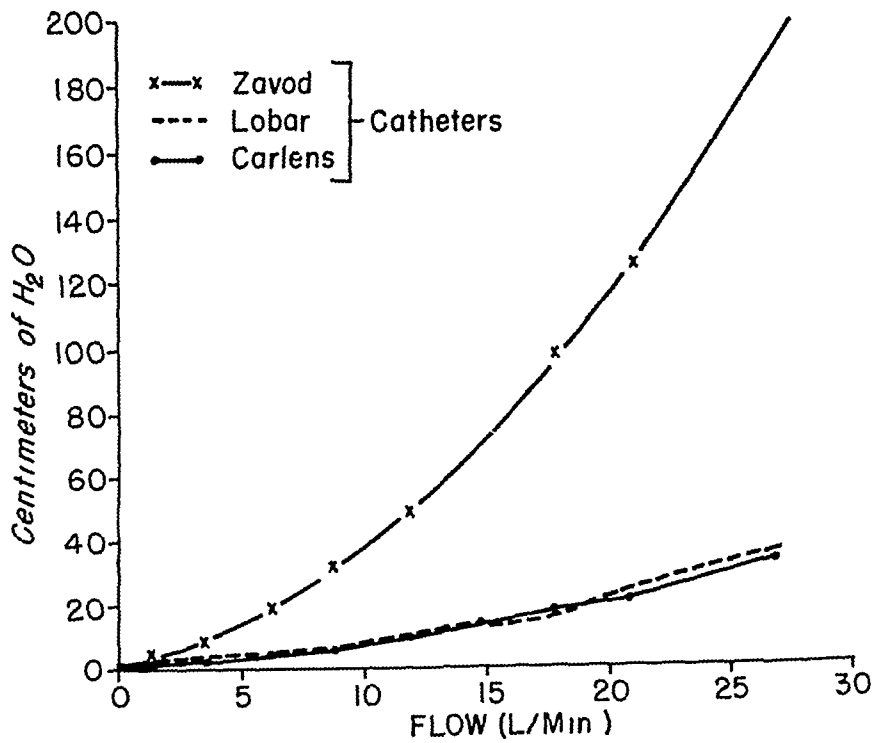


FIGURE 2 Flow characteristics of the lobar spirometric catheter and left side lumen of two standard catheters (Zavod and Carlens) Upper- and lower-lobe lumina combined on the lobar spirometric catheter

Similar comparison of tracheal lumina of the three catheters results in a plot of flow resistance similar to that in Figure 2 The same general relationship among the three catheters in the same ranges of value is also found when flow and pressure in the short lumina are measured

Possible Uses for Lobar spirometry

This lobar spirometric catheter was originally designed for specific research purposes, and the experience gathered during its use in 25 right-sided and 5 left-sided lobar studies confirms its usefulness in such areas as the investigation of pressure volume gradients, the mechanics of lung motion, and the study of perfusion differences accompanying changes in body position

However, our experience also indicates that this catheter may be used to provide data available in no other way Thus, in those patients whose pulmonary function is severely reduced, data obtained by use of this catheter may allow salvage by pulmonary resection Also, this catheter can often be used when abnormalities of the tracheobronchial tree prohibit the use of the standard bronchospirometric procedures

SUMMARY

We have described a new three-lumen catheter designed to allow oxygen uptake and ventilatory studies to be simultaneously performed on the upper and the lower lobe of one lung and on the entire contralateral lung Some general areas where this catheter may be very useful have been indicated

RESUMEN

Hemos descrito un catéter de tres luces ideado para permitir el ingreso de oxígeno y hacer estudios ventilatorios simultáneamente en los lóbulos inferior y superior de un pulmón y en el contralateral completo Se señalan algunas indicaciones útiles para este catéter

RESUME

Les auteurs ont décrit un nouveau cathéter à trois lumières établi pour permettre l'arrivée d'oxygène et des études ventilatoires portant simultanément sur le lobe supérieur et inférieur d un poumon et sur la totalité de l'autre poumon Les auteurs ont donne quelques indications générales pour lesquelles cette sonde pouvait être de grande utilité

ZUSAMMENFASSUNG

Wir haben einen neuen Katheter mit drei lumina beschrieben, der die Aufgabe hat, die Sauerstoffaufnahme zu gestatten und ventilatorische Studien gleichzeitig vom oberen und unteren Lappen einer Lunge und der ganzen kontralateralen Lunge zu ermoglichen Es wurden einige allgemeine Anwendungsgebiete aufgezeigt, bei denen dieser Katheter eine nutzliche Verwendung finden kann

REFERENCES

1 Breton, A and Mereau, J "Interet des Epreunes Fonctionnelles Respiratoires par Airs Separes en Chirurgie Thoracique," *Le Poumon*, 3 335, 1947
2 Carlens, E and Mattson, S B "Lobar Ventilation and Oxygen Uptake in Man Influence of Body Position," *J Thoracic Surg*, 30 676, 1955
3 Martin, C J, Cline, F and Marshall, H "Lobar Alveolar Gas Concentrations, Effects of Body Position," *J Clin Investigation*, 32 617, 1953

The Use of Trypsin in the Therapy of Tuberculous Lymphadenitis and Tuberculous Fistulae*

CHAIM RAPOPORT, M D *,*

Beer Yacov, Israel

This report deals with nine cases of tuberculous lymphadenitis treated with trypsin in sesame oil and uninterrupted antituberculosis drugs Follow-up periods varied from eight to 16 months, including histopathological evaluation of the results of treatment

Antituberculous drugs in tuberculous lymphadenitis have been in general disappointing The natural course of tuberculous lymphadenitis with its alternating periods of quiescence and relapse make it difficult to evaluate those few cases that have met with apparently successful treatment The disappointment is more deeply felt as other forms of primary tuberculous and fresh exudative lesions have responded so well to the drug now in use We felt that any additional factor that will enhance the phagocytic power of the mononuclear cells[1, 5, 4] and open up vascular channels to the site of the causative factor of the disease for the drugs in use may be helpful in overcoming the infection [2, 6] With this in mind, pure crystalline trypsin in sesame oil,† each ml containing 5 mg, was administered intramuscularly simultaneously with various antituberculous drugs

Methods

We selected only those cases where unequivocal evidence of tuberculous etiology was present and which under prolonged drug treatment did not improve or become progressively worse In every case we had biopsy or culture for Koch's bacillus before the start of treatment, where feasible during treatment, and in all cases at the end of treatment Each case had x-ray films of the neck, chest, spine and appropriate bones Routine blood studies, urine examinations, liver function tests, and ECG were performed at the start, during, and on termination of treatment The cases were examined daily on the ward Trypsin was administered intramuscularly in combination with one or more of the following Rimifon, para-aminosalicylic acid and streptomycin

Case 1 P Sh Hospital No 30074 This girl of eight years was referred to our hospital because of masses in the right axilla with multiple draining sinuses and a protruding fluctuating mass below the right clavicle Tissues were indurated and edematous She had been hospitalized from March 1953 until July 1954 because of tuberculous lymphadenitis colli and because of multiple cold abscesses located in various parts of the chest and right axilla X-ray films of the chest in 1953 showed enlarged mediastinal lymph nodes as well as atelectasis of the anterior segment of the right upper lobe She had received a total of 18 Gm Rimifon and 2 2 kg of PAS Her general condition was improved following treatment, the sedimentation rate dropped from 80 mm per hour to 10 mm per hour upon discharge *The draining fistula closed* While in the

This report is based on work done in Malben's Tuberculosis Hospital in Israel, which is supported by the American Joint Distribution Committee which receives its funds through the United Jewish Appeal

*Head of Department, *Malben's Tuberculosis Hospital*

†Parenzyme The National Drug Company, Philadelphia, Pennsylvania

outpatient clinic, the enlarged nodes in the right axilla reappeared, the fistula re-opened and the discharge was positive for Koch's bacillus on culture

Local PAS ointment was given without success and she was admitted to our hospital in May 1955 She was toxic, and her temperature was 39-40°C Physical examination revealed a large mass in the right axilla, consisting of multiple matted nodes, and numerous draining fistulae In addition, a large swelling (6x8 cm in diameter) was present below the right clavicle X-ray films of the chest, spine, neck, and ribs were negative Puncture aspiration of the abscess below the clavicle revealed pus which contained Koch's bacilli Swabs from the sinuses showed Staphylococcus aureus, coagulase positive, sensitive to Achromycin Treatment with Achromycin was started, following which the temperature dropped to normal and her general condition improved However the local appearance of the lesions remained unchanged Drainage from the sinuses continued unabated After eight cultures came back positive for Koch's bacillus, including two guinea pig inoculations, on June 29, 1955, simultaneous treatment with Rimifon and trypsin was started Trypsin was given intramuscularly for 10 days (a total of 50 mg, 5 mg daily in two divided doses) Rimifon was continued for an additional two weeks after stoppage of the trypsin, a total period of Rimifon administration was 24 days, totalling 3 gm On the sixth day of treatment the old fistulae were almost closed and the new fistulae formed at the base of puncture of the fluctuating mass below the right clavicle started healing with healthy granulation tissue at its base By the end of July 1955, which is one month after initiation of treatment, all fistulae were closed and replaced by firm scar The mass in the right axilla decreased markedly, only rudimentary small nodes were palpable in that region, sedimentation rate dropped from the original 50 mm to 16 mm per hour She remained clinically well and under observation in the hospital

In December, 1955, in view of the contemplated biopsy of the residual nodes, Rimifon was re-started on a daily dosage of 150 mg and continued until March 18, 1956, on which day the residual nodes were removed The histological report follows Fibrosis of lymph nodes without histological evidence of tuberculosis Concentration and culture for Koch's bacillus as well as guinea pig inoculation removed at the biopsy from different areas were negative

For the last seven months she has been clinically well

Case 1

Case 2 A B Hospital No 36285 This girl of 13 years had a swelling detected in the right side of the neck in January 1955 This gradually enlarged and she was referred to the Chest Clinic with the diagnosis of tuberculous lymphadenitis colliis X-ray film of the chest showed calcified nodes in the right hilum as well as a calcification in the apex of the lower lobe of the right lung X-ray film of the neck showed multiple calcifications bilaterally On physical examination a fluctuating mass beneath closely knitted nodes was palpable Aspiration in March 1955 revealed pus that was sterile on general culture and negative for Koch's bacillus Following aspiration a draining fistula appeared This was treated for two months with Rimifon and PAS, a daily dosage of 150 mg and 5 gm respectively A total of 7 gm Rimifon and 500 gm PAS was given until transfer to our ward On admission in June 1955 a continuously draining fistula was present Underlying it was a big palpable node The area surrounding the fistula was red and edematous After two weeks of observation without treatment and without change in the local condition, trypsin, 5 mg daily, and Rimifon, 150 mg daily, were administered On the fourth day of treatment the fistula was closed and crusted Trypsin was given for seven days and Rimifon 14 days A firm scar was seen after three weeks of drug She remained in the hospital for nine months without additional treatment The scar remained firm, the underlying node became small but palpable After nine months of observation the nodes were removed

Histo-pathological studies revealed eosinophilic staining clumps which appeared to be disintegrating acid-fast bacilli Tuberculous lymphadenitis active

Culture for Koch's bacillus and guinea pig inoculation of the biopsy material were negative

The wound healed, and she was discharged clinically well after three months' additional hospital observation and remained so until December, 1956

Case 3 A T Hospital No 33419 This girl of five years was hospitalized in another institution from August 30, 1954 to January 16, 1955 She was admitted to the a/m institution because of extensive tuberculous cervical and mediastinal lymphadenitis with secondary atelectasis in the right lower and middle lobes Her general condition was poor On extensive combined antituberculous drugs including local administration there was little improvement She had 28 gm of streptomycin, 5 gm Rimifon, and 250 gm PAS Biopsy of cervical nodes and those of the groin showed active tuberculous lymphadenitis Following biopsy the wound remained open and drained for a long time She was admitted to our ward in January 1955 with the findings above described It was decided to keep her under observation without drugs for eight months During this period she led a normal life and attended kindergarten and the clinical condition markedly improved She gained weight, developed mentally, the nodes in the neck and mediastinum decreased in size and were hardly palpable in the exposed region In September 1955 antituberculosis drugs were started because of appearance of productive cough Rimifon, 100 mg, and streptomycin, 1/4 gm every third day, were given In March 1956, while she was still receiving drugs, lymph nodes enlarged in the submaxillary and left axillary regions A submaxillary node region removed on April 9, 1956 showed evidence of tuberculous lymphadenitis with extensive caseation and recent liquefaction Smudges of eosinophilic staining were present, which appeared to be disintegrating tubercle bacilli On April 9, trypsin was added in a dosage of 5 mg daily to the previously administered antibiotics and continued until May 6, 1956 A total of 75 mg of trypsin was administered On May 6, 1956, the node in the left axilla which decreased in size during the period of treatment was removed for biopsy This revealed chronic lymphadenitis, evidence of tuberculosis Cultures and guinea pig inoculation were negative for Koch's bacilli Trypsin and antituberculosis drugs were continued and the large node in the submaxillary region, adjacent to the one biopsied on May 9, 1956, was markedly decreased in size On May 20, 1956, or three weeks after initiation of the treatment, node was removed (A total of 100 mg of trypsin had been given)

It contained granulomatous lesion with considerable fibrosis, apparently tuberculous

Culture and guinea pig inoculation were negative

She has remained clinically well without treatment for the last eight months

Case 4 O S Hospital No 30087 This girl of 10 years was hospitalized for the first time in December 1951 because of cervical and mediastinal tuberculous lymphadenitis From December 1951 until January 1955 she received interrupted combined antituberculos s drugs (total of 1 5 Kg PAS, 20 gm streptomycin, and 15 gm of Rimifon) in addition to x-ray therapy, heliotherapy and local PAS application to draining fistula On admission to our hospital in January 1955 multiple cervical nodes varying from 5 to 25 mm in diameter were present in addition to scars of previous sinuses No special treatment was administered until May 1956 During this one and one-half years of observation, the cyclic nature of the appearance of the cervical nodes was confirmed Every four and one-half to six months the nodes had previously enlarged, reached a maximum size, and subsided within four to six weeks On May 7, 1956,

biopsy of a node revealed a granulomatous lesion, probably tuberculous Complete bacteriological studies were negative for Koch's bacillus

On May 9, 1956, she was started on trypsin, 5 mg daily in two divided doses, Rimifon, 100 mg daily, and streptomycin, 1/4 gm every third day During the next four months the antituberculosis drugs were given but trypsin was discontinued after 46 days Marked clinical improvement took place and most of the nodes disappeared Biopsy on September 3, 1956 revealed fibrosis in addition to changes of chronic inflammation, non-specific in the small nodes and areas of caseation, partially surrounded by fibrous capsules with evidence of specific granulation tissue with epithelioid cells and giant cells of Langhans' type in the large nodes

Case 5 F R Hospital No 396669 This girl of 10 years was admitted to our ward on June 4, 1956 Previous to admission she had received 100 mg of Rimifon daily since April 1956 On admission a large profusely draining crater was overlying the second portion of the sternum The process was in the first and second portion of the sternum with marked periostial reaction X-ray film revealed enlarged mediastinal lymph nodes and soft infiltrations bilaterally Pus from the draining ulcer contained Staphylococcus aureus coagulase positive and C diphtheriae sensitive to all antibiotics

On July 6, 1956, the lesion appeared unchanged and trypsin (5 mg daily in two divided doses) together with Rimifon (150 mg daily) and PAS (6 gm daily) were started On August 8, 1956, a firm scar was present in the place of the previous deep crater and x-ray film of the sternum, dated August 1, 1956 (three weeks after start of treatment), showed marked sclerosis of the bone lesion and striking decrease in periostial reaction A total of 85 mg of trypsin was given

Case 6 M B Hospital No 34181 This boy of five years was referred to our hospital because of tuberculous lymphadenitis collis with draining fistulae He had been under treatment since 1951 and had received, until May 1954, 60 gm of streptomycin, 1 Kg of PAS, as well as 12 x-ray radiations with only temporary relief From May 1954 he had received Rimifon and PAS without improvement When admitted here on November 1, 1955 he had large left cervical masses with multiple draining sinuses and at the angle of the jaw on the same side X-ray film of the neck showed large calcified nodes bilaterally with surrounding area of tumefaction His temperature was 39-40°C and he was highly toxic Trypsin, 5 mg daily, in two divided doses, together with Rimifon, 150 mg daily were started November 28, as there was no improvement since admission Three weeks after this treatment was started the sinuses were closed and the masses were strikingly diminished On March 1, 1956, trypsin

Case 6

was stopped and Rimifon continued until March 2, 1956 At the time the trypsin was stopped, firm scars existed in the place of the previous sinuses A total of 150 mg of trypsin had been given up to this time On April 3, 1956, trypsin was re-started in the previous dosage preparatory to the intended biopsy of the underlying nodes Biopsy on May 20, 1956, revealed two groups of nodes The large calcified node showed a minimal activity tuberculosis process while the lymph nodes underlying the scar contained only lymphoid hyperplasia Multiple smears, cultures, and guinea pig inoculations of the biopsied material (both groups) were negative for Koch's bacillus

On July 3, 1956, trypsin was added to the antituberculosis drug in use and continued until September 3, 1956 Then two nodes were removed from the right side of the neck, which were reported as calcified on admission The small gland showed evidence of chronic non-specific inflammation, with proliferation of the reticuloendothelial system The large node showed evidence of chronic non-specific inflammation, at the periphery, as well as proliferation and enlargement of the lymph follicles In the center a wide area of caseation surrounded by wide mantle of fibrosis was seen No specific granulation tissue was identified

Case 7 S H Hospital No 37372 This man of 33 years was admitted to our hospital on October 7, 1955 In May 1951 a large mass appeared under the right clavicle This fluctuating mass burst open and drained continuously In May 1955, after Koch's bacillus was found antituberculosis drugs were started and 36 gm of Rimifon, 700 gm of PAS, and 4 gm of streptomycin had been administered An x-ray film of the chest at that time showed involvement of the first rib on the right side In our hospital on November 1, 1955, tuberculous granulation tissue was removed behind the first rib, partial resection of the first rib was performed, and wide excision of the tracts was done

Culture for Koch's bacillus of this granulation tissue was positive for Koch's bacillus Following operation wound healed He received a total of 62 gm of streptomycin and 18 gm of Rimifon In January 1956 the wound was closed when he was discharged On March 15, 1956, he was readmitted because of multiple draining fistulae at the site of the operation The remaining segment of the first rib removed, and the fistula tract excised on March 18, 1956 and tuberculous granulation tissue was found

The fistulae remained open and discharging pus, although PAS, streptomycin, and Rimifon daily were continued to a total of 87 gm of streptomycin, 108 gm of Rimifon, and 250 mg PAS, not counting the amounts of antibiotics given to him from May until October 1955 in the outside institutions

On the first of August, 1956, trypsin was added in a dosage of 5 mg daily in two divided doses to the combined antituberculosis drugs After three weeks the fistulae were filled in with healthy granulation tissue and by the end of six weeks firm scars were present

Case 8 M H Hospital No 39632 This boy of 12 years was referred to us from another institution on June 3, 1956 He received 51 gm of streptomycin and 600 gm of PAS from March 30, 1956, until May 30, 1956 On admission he had enlarged nodes in both axillae with multiple scars X-ray film of the spine showed destruction of vertebrae from D3 to D6 as well as a cold abscess Antituberculosis drugs were continued including 4 gm of Rimifon, 2 gm of streptomycin, and 140 mg of PAS On June 23, 1956, a lymph node was removed from a large packet of glands in the right axilla This contained a cavity lined by a broad zone of tuberculous granulation tissue surrounded by lymphocytic infiltration and wide mantle of fibrosis No acid-fast bacillus was seen

Culture and guinea pig inoculation were negative Following biopsy trypsin was given for two months in a dosage of 5 mg daily together with the antituberculosis drug

On September 4, 1956, no lymph node could be visualized on dissection

No acid-fast bacilli on smear A lump removed proved to be subcutaneous tissue attached to skin A few foci composed of epitheloid cells and giant cells of Langhans' type were present but there was no caseation Acid-fast bacilli were not found The wound healed per primam

Case 9 T A Hospital No 33083 This girl of five years was admitted on January 23, 1955, without available history A large group of nodes was visible overlying the right parotid area They were swollen and tender The skin edematous and inflamed Trypsin *without* antituberculosis drugs was given for one week with marked subsidence of the inflammatory reaction Between September 15, 1955, and April 19, 1956 she received 15 gm of streptomycin and 17 gm of Rimifon On April 19, 1956, a removed node revealed extensive caseation with focal calcification, the surrounding reaction of tuberculous granulation tissue was narrow, and there was slight fibrosis Drugs were continued as before, and trypsin was added from June 1956 until September 4, 1956, in usual dosage

On September 4, 1956, a lymph node showed marked proliferation of the lymph follicles In the center of the node specific granulation tissue partially caseated was

seen surrounded by collagen Acid-fast bacilli were not found on smear At the time of the last biopsy doubt existed in the surgeon's mind whether any node was left for excision

SUMMARY AND CONCLUSIONS

1 Seven cases of tuberculous lymphadenitis and two cases of bone tuberculosis (sternum and first rib) with tuberculous fistulae were treated

2 All had previous antibiotic treatment without success for periods varying from four months to four years

3 Treatment with trypsin given simultaneously with antibiotics effected a clinical cure within a period varying from three to six weeks

4 Clinical healing was evidenced by a marked decrease in size of nodes, disappearance of nodes, closure of fistulae and scar formation This does not imply cure from the histo-pathological point of view

5 Bone tuberculosis healed more rapidly

6 *From a histo-pathological point of view all the biopsies performed at* intervals and at the end of treatment showed either marked improvement of the histological picture or evidence of complete healing The rich deposition of collagen in healed lesions is noteworthy The material of the biopsied nodes at the end of treatment was negative on smear, culture and guinea pig inoculation for Koch's bacillus

7 The schedule of treatment advised is as follows Trypsin 5 mg daily in two divided doses for six weeks, simultaneously with uninterrupted antibiotics, Rimifon and PAS daily for six months An additional course of trypsin of three weeks' duration at the termination of the six months' period No side effect was noted during treatment

8 *Trypsin administered together with antibiotics appears to be the treatment of choice of tuberculous lymphadenitis and tuberculous sinuses, secondary to the above, or bone tuberculosis*

CONCLUSIONES

1 Se trataron siete casos de linfadenitis tuberculosa y dos de tuberculosis ósea (esternón y primera costilla), con fístula

2 Todos habían tenido tratamiento con antibioticos de cuatro meses a un año antes

3 El tratamiento con tripsina dado simultáneamente con los antibióticos logró una cura clínica dentro de un término variando de tres a seis semanas

4 La curacion clínica se evidenció por un marcado decrecimiento del tamaño de los ganglios, desaparicion de ellos, cierre de fístulas y formación de cicatrices Esto no implica curación desde el punto de vista histopatológico

5 La tuberculosis ósea curó más rápidamente

6 Desde el punto de vista histopathológico, todas las biopsias realizadas a intervalos y al final del tratamiento mostraron ya sea mejoría o evidencia de curación Es de notarse la elevada acumulación de colágena en las lesiones curadas

El material de los ganglios a la biopsia al fin del tratamiento fué negativo al frotis, cultivo e inoculación al cuy, para el bacilo de Koch

7 El tratamiento es como sigue Se dan 5 mg de tripsina diarios en dos

dosis por seis semanas simultáneamente con antibióticos sin interrupción, Rimifón y PAS diariamente por seis meses Una serie adicional de tripsina por tres semanas se da al terminar el período de seis meses No se notaron efectos colaterales

8 La tripsina administrada junto con los antibióticos parece ser el tratamiento de elección de la linfadenitis tuberculosa, así como de las fístulas tuberculosas secundarias a la anteriori o de la tuberculosis ósea

RESUME

1 L'auteur a traité sept cas d'adénopathies tuberculeuses et deux cas de tuberculose osseuse (sternum et première côte) avec fistules

2 Tous avaient reçu un traitement antibiotique sans succès pendant une période de 4 mois à 4 ans

3 Le traitement par la trypsine associée aux antibiotiques amena la guérison clinique dans un laps de temps de 3 à 6 semaines

4 La guérison clinique fut objectivée par la décroissance nette de la taille des ganglions, leur disparition, la fermeture des fistules et la constitution d'une cicatrice Ceci ne veut pas dire qu'il y ait guérison complète au point de vue histologique et anatomo-pathologique

5 La tuberculose osseuse évolua plus rapidement vers la guérison

6 Du point de vue histologique et anatomo-pathologique, toutes les biopsies pratiquées à intervalles réguliers et à la fin du traitement montrèrent soit une amélioration nette des aspects histologiques soit une guérison complète La présence d'un dépôt abondant de collagène dans les lésions guéries mérite d'être noté Les produits de biopsie ganglionnaire en fin de traitement ne contenaient plus de bacilles de Koch décelables soit par frottis, soit par culture, soit par inoculation au cobaye

7 Le programme du traitement qui a été suivi est le suivant trypsine 5 mmg par jour en deux doses pendant six semaines, associée aux antibiotiques Rimifon et P A S administrés de façon ininterrompue chaque jour pendant six mois Une série supplémentaire de trypsine d'une durée de trois semaines à la fin de six mois On ne nota aucun effet secondaire pendant le traitement

8 La trypsine administrée avec les antibiotiques semble être le traitement de choix des adénopathies tuberculeuses et des fistules qui peuvent leur faire suite ainsi que de la tuberculose osseuse

SCHLUSSFOLGERUNG

1 7 Falle von tuberkuloser Lymphadenitis und 2 Falle von Knochentuberkulose (Brustbein und erste Rippe) mit tuberkulosen Fisteln wurden behandelt

2 Alle hatten zuvor eine antibiotische Behandlung gehabt, die ohne Erfolg geblieben war und zwar in Zeitsbschnitten zwischen 4 Monaten und 4 Jahren

3 Behandlung mit Trypsin in Verbindung mit Antibioticis bewirkte eine klinische Heilung in einen Zeitraum von 3-6 Wochen

4 Klinische Heilung wurde augenscheinlich gemacht durch eine ausgesprochene Abnahme in der Grosse der Knoten, einem Verschwinden der Knoten, Fistelverschluss und Narbebildung Dies besagt nicht Heilung vom pathologisch-histologischen gesichtspunkt

5 Knochen tuberkulose heilte schneller

6 Vom pathologisch-histologischen Standpunkt gesehen, zeigten alle in Intervallen und am Ende der Behandlung durchgefuhrten Biopsien entweder eine ausgesprochene Besserung des histologischen Bildes oder den Augenschein einer kompletten Heilung Die reichliche Ablagerung von Bindegewebe in geheilten Herden ist bemerkenswert Das Material der Biopsien der Lymphknoten am Ende der Behandlung war auf Koch'sche Bazillen negativ im Ausstrich, in Kutur und Tierversuch

7 Das empfohlene Behandlungschema besteht in Trypsin 5 mmg tagl in zwei geteilten Dosen auf 6 Wochen gleichzeitig mit pausenlosen Antibioticis, Rimifon und PAS taglich auf 6 Monate, eine zusatzliche Folge von Trypsin von drei Wochen am Ende der ½-Jahres-Periode Es wurden keine Nebenwirkungen wahrend der Behandlung beobachtet

8 Trypsin bei Verwendung in Verbindung mit Antibiotics scheint die Behandlung der Wahl zu sein bei der tuberkulosen Lymphadenitis und bei tuberkulosen Fisteln als Folge derselben, oder bei Knochentuberkulose

REFERENCES

1 Innerfield, L , Angrist, A and Schwarz, A "Parenteral Administration of Trypsin Clinical Effect in 538 Patients," *J A M A* , 152 597, 1953

2 Ponder, E "Effects Produced by Trypsin in Certain Properties of Human Red Cell," *Blood*, 6 350, 1951

3 Innerfield, I , Angrist, A and Benjamin, J W "Studies on Trypsin, Anticoagulant Action of Trypsin," *Gastroenterol* , 20 630, 1952

4 Innerfield, I , Schwarz, A and Angrist, A "Intravenous Trypsin Its Anticoagulant, Fibrinolytic and Thrombolytic Effects," *J Clin Invest* , 31 1049, 1952

5 Innerfield I "Trypsin Given Intramuscularly in Chronic Recurrent Thrombophlebitis," *J A M A* , 156 1056, 1954

6 Tabachnick, J and Weiss, C "Mechanism of Softening of Tubercles IV Digestion of Caseous Tubercles by a Proteinase Extracted from Polymorphonuclear Leucocytes," *A M A Arch Path* , 61 76, 1956

The Endoscopic Treatment of Parenchymal Tuberculosis

(A Pilot Study in the Human)

A ALBERT CARABELLI, M D, F C C P
Trenton, New Jersey

To date the therapy of pulmonary tuberculosis has been more or less confined to three main categories compression, extirpation, and chemotherapy There have been many variations of each procedure and frequently any of the three have been used in combination The selection of the particular type of therapy or combination has been more or less standardized and to date one sees pneumothorax on the wane, extirpation on the rise, and chemotherapy predominant

With respect to chemotherapy, review of the literature shows that the trend is towards the almost universal use of isonicotinic acid hydrazide (INH) in combination with streptomycin (SM) or para-aminosalicylic acid (PAS) Dosage of these drugs has been commonly accepted at 4 mg/K, 1-2 grams/week, and 12 grams/day, respectively

It is interesting to review the literature to date on the chemotherapeutic results in parenchymal tuberculosis, pointing out the salient features and the gross averages in results All the authors reviewed[1, 2, 3 4, 5] have used INH alone or in combination with SM or PAS in the dosage indicated above The period of treatment varied from one to 32 months Sputum conversion was from 5-100 per cent with any increase more or less proportionate to the length of time treated In all cases the determination of negativity depended on *expectorated* spittles or on *gastric studies* With respect to the constitutional symptoms all authors are in accord with the usual increase in weight, subsidence of toxic manifestations, and the general beneficient effect of INH on the body and psyche With respect to the x-ray film changes there is reported an over-all improvement in about 60 per cent of cases Cavity closure was noted in about 30 per cent and diminution in size in 21 5 per cent Clearing of the exudates was recorded at 24 per cent There is general agreement that fibrous lesions, calcified areas, thick-walled cavities and old fibro-caseous foci remained unchanged, and that, in many instances, little change is noted in the x-ray film status of the lesion in spite of the conversion, weight gain and sense of well-being Most of the improvement, often with dramatic clearing, is noted in the recent lesion of an exudative nature Another axiom in the roentgen observations is that if any im-

Presented at the IV International Congress on Diseases of the Chest, Cologne, Germany, August, 1956

Chief of Thoracic Medicine, St Francis Hospital, and Consultant in Thoracic Medicine and Bronchoesophagology, Trenton General Hospital, Trenton, N J Formerly Associate in Medicine, Graduate School of Medicine, University of Pennsylvania, *Philadelphia, Pennsylvania*

provement occurs, this takes place in the first three months and then such changes become progressively fewer and of lesser degree

The following study concerns the exploration of an entirely new approach in the chemotherapy of parenchymal tuberculosis namely, the *endobronchial* route This concept is relatively new and few references are to be found in the literature[6,7] Before going into the details of its clinical aspects, however, it is important to outline certain basic anatomico-physiological as well as pathological phases of the fate of particulate matter within the lung Special reference is made to the tubercle bacillus as well as the antituberculosis characteristics of several drugs for a better understanding of the rationale of this type of therapy

Studies of the fate of particulate substances including the tubercle bacillus[9] introduced into the respiratory channels show a definite reaction on the part of the host to such invasion The portion of this matter not immediately removed by cough penetrates the air passages and is carried to their finest subdivisions where it is subjected to reactions brought about by the protective forces indiginous to normal tissues Phagocytosis is the first to function but is limited to particles less than 10 microns in size The larger particles are not engulfed, they are promptly removed through the airways by the usual excretory function of entrapment in mucous secretions, ciliary motion, molding by the spiral bronchial musculature, and the expellent force of cough Three cells—the polymorphonuclear leukocyte, the mononuclear alveolar cell, and the mononuclear cell which is believed to come from the blood—are the phagocytes concerned in removing particulate matter from the parenchyma, and this is done by way of the lymphatics One mechanism is by way of the *superficial lymphatics,* which follow the first radicle of the pulmonary vein from the center of the primary lobule to its periphery and then course outward to join the subpleural plexus which in turn unite to form the lymph vessels that empty into the hilar nodes The second is by way of the *deep lymphatics,* which follow the bronchial and vascular channels towards the hilar lymphnodes Still a third method of excretion through the alveolar ducts, bronchioles, and bronchi exists but does not concern us in this study since it is non-contributory to the concentration of the drug in the parenchyma or lymphatics

Once started, the lymphatic removal of particulate matter is rather rapid as can be seen following the introduction of graphite in the trachea when this substance will appear in the paratracheal nodes in about an hour Tubercle bacilli similarly introduced have been culturally recovered from various organs 12 hours after introduction

The superficial lymphatic route may be demonstrated by the presence of cells crowded together into irregular, ill-defined groups spaced at irregular, intervals along the course of the radicles of the pulmonary vein and in the subpleural lymphatic tissues In these situations permanent lesions develop as anatomic tubercles when the foreign substance is the tubercle bacillus The route of the deep lymphatics may be similarly traced by the temporary and permanent grouping of the phagocytic cells

along their course and also by observing the bronchial lymph follicles through and around which the lymphatics course Often these vessels are crowded with degenerated phagocytic cells being carried out of the lung

These observations would indicate that the introduction of particulate matter of antituberculosis activity directly into the bronchi would follow the same route taken by the tubercle bacillus and thus introduce bacteriostatic or bactericidal agents directly into foci usually involved by tuberculous infections With such a portal of entry several advantages are obvious firstly, a very high focal concentration of the drug may be possible which would remain in the lobe for an indefinite period (oily suspension), secondly, phagocytes loaded with engulfed drug particles are made the bearers of the noxious agent to the tuberculous foci proper and, with their death, release a therapeutic bomb, thirdly, bacilli-laden phagocytes will transport only non-viable bacilli to new foci since INH,

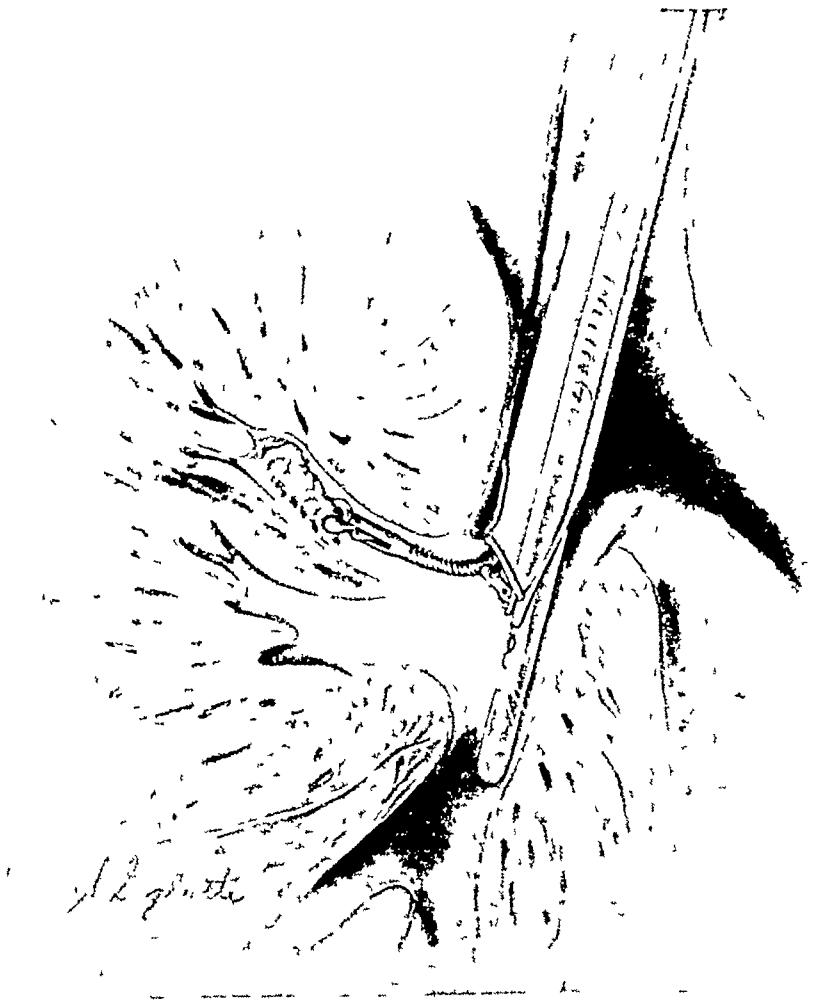


FIGURE 1 Upper lobe instillation with the Pentascope This figure shows the instrument being used for biopsy In instillation techniques a flexible woven catheter is substituted in lieu of forceps Note possibility of segmental bronchus visualization and catheterization In this case the apical segmental bronchus of the right upper lobe has been entered

unlike SM, readily penetrates cell membranes in effective bacteriostatic or bactericidal concentration [10 11]

From the experimental animal and human studies[10 11] it may be concluded that the oral administration of INH results in its concentration in the body fluids and plasma in direct proportion to any given dose whether in single or chronic administration, and that its retention is non-cumulative since it is rapidly excreted from the urine, faeces, and saliva The same studies indicate that the safe dose for chronic administration in man is an oral dose of 3-4 mg /K per day, which will result in a plasma concentration of 1 3-3 4 gamma/ml The incidence of toxic reactions above these levels seems to be in direct proportion to the increased dosage

It is obvious, that with the conventional oral dose, we are distinctly limited as to the amount of the drug which can be used safely If we attempt to increase the dose on the supposition that a higher plasma concentration will have a stronger anti-tuberculosis effect, we are faced with a therapeutic frustration Now, if the lung proper could be used as a therapeutic portal, we might be able to increase the concentration of the drug at the site of the disease without saturating the body as a whole and thus avoid any systemic toxic reactions Such a concept might be feasible if a slowly absorbed preparation could be used which would saturate the lobe or lobes and still be ineffective in raising plasma levels to toxic thresholds Herein lies the *concept of lobar or multi-lobar rather than body saturation*

In the lung we have an anatomic *cul-de-sac* not equipped by nature for the rapid absorption or the chemical alteration of foreign substances as is the case with the intestinal tract Physiologically the lung is highly specialized for gaseous exchange only, and for these purposes has a tremendous surface area It also has a great potential for phagocytosis because of its richness in capillaries and lymphatics It has been possible to instil substances of low absorption characteristics such as penicillin in oil into these passages with considerable clinical success (12), and it has long been known that such substances as lipiodol remain in residence for many months without any harm to the parenchyma proper or detectable impairment to the lobar physiology

From the technical point of view it is presently possible to instrumentally reach many of the segmental and certainly all of the lobar bronchial levels for practical instillation of such substances

It is interesting, on a purely gross theoretical basis, to calculate the drug concentration in one milliliter of lobar fluid when 10 cc of an oily suspension containing 500 mg of INH is introduced into a lobar bronchus Using 991 grams as the average weight of the human lungs (33) and then considering the presence of six lobes by assuming the lingular division as a separate lobe, we arrive at an average lobar weight of 165 grams Assuming that 90 per cent of this tissue is liquid matter, we could have a total of 148 5 mls which eventually pick up 500 mgm of INH This would be equivalent to 3367 gamma/ml of the drug Again, on the assumption that 75 per cent is lost through the alveolar ducts, bronchioles, and bronchi, as well as dissipated to other organs and tissue fluids by

the blood stream, there might be, at any one time, a potential level of saturation of 842 gamma/ml in the lobe concerned, uniformly disseminated according to the laws of osmosis, mass action, and phagocytosis When this concentration is compared with the normal ranges of 1 3-3 4 gamma/ml (plasma) obtained by standard oral medication, we can readily see the advantage of such a therapeutic portal if the clinical findings, host, and parenchymal tolerance, could justify such a procedure

Another interesting observation in this respect is that animal studies[14] indicate that INH is broken down into isonicotinic acid and ammonia by enzymatic action in most organs, but that is not true in the lung (rat) If a parallel situation holds in the human, we have this added advantage to the use if the lung as a therapeutic portal

Selection of the Drug of Choice

The fact that the preponderance of the literature in the chemotherapy of pulmonary tuberculosis centers about INH indicates that this particular

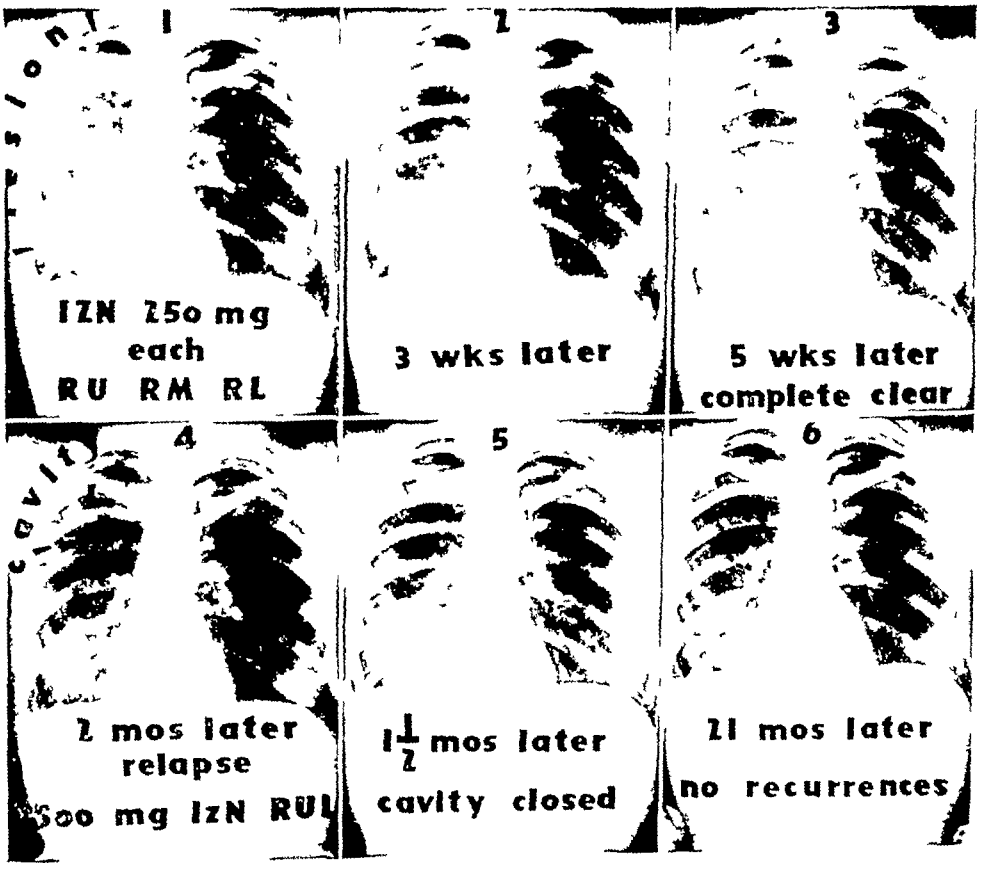


FIGURE 2 H G, a white female, age 21, with a history of right-sided pulmonary tuberculosis treated successfully with pneumothorax from 1950 to 1952, when pneumothorax was discontinued Patient well and on full duties until 1954 when she developed a recurrent far-advanced ipsolateral lesion Bronchial aspirate was positive for tubercle bacilli Note very rapid clearing of the lesion within an interval of 5 weeks following the instillation of endobronchial INH This patient was on concomitant oral INH and PAS in full doses, but in spite of this she developed a cavitational lesion 2 months following the complete regression of the original massive lesion The cavity disappeared completely in 1½ months following a second endobronchial instillation Note complete restitution to normal of the parenchyma except for the basal diffuse cloudiness which represents pleural thickening following the abondonment of the original pneumothorax

drug has definitely proved its antituberculosis effect clinically It has the advantage of low toxicity even when administered over a long period of time With respect to strains resistent to SM it is more effective because of its ability to penetrate the cell membrane in effective concentration which is not true of SM [10, 11] For example, a concentration of 0 05 gamma/ml of INH will prevent the growth of H37Rv strains when compared with 25 gamma/ml in the case of SM This latter concentration is therapeutically not possible

Resistance studies[8] indicate that most strains of the tubercle bacillus become resistant to INH in from two to four months, which probably accounts for the rather dramatic initial systemic as well as roentgen changes which taper off as the time of its use is increased When combined with PAS, however, resistance is much longer in developing and much longer than when combined with SM In the present study this combination was not used as it was the intent to study only one drug

Following study of the various available preparations of INH, a lyophilized form manufactured by the Panray Corporation of New York was found most suitable This preparation comes in sterile vials containing 1 gram of the drug The addition of 20 cc of sterile olive oil and shaking well resulted in the *basic suspension* used in this study This suspension is easy to work with and readily instilled with the catheters and instruments devised A 15 or larger gauge needle facilitates aspiration into a standard syringe The *radiopaque suspension*, the use of which will be described later, is made by adding 10 cc of sterile olive oil and 10 cc of Dionosil to the 1 gram vial of INH

Bronchographic and Bronchoscopic Observations on Behaviour of Oily Substances in the Lung

General observations in the use of oily contrast and therapeutic media in the lung indicate that such substances have little deleterious effect on the parenchyma (not true of mineral oils), and furthermore, that such preparations may remain safely in residence for many months as can be appreciated from the study of films following lipiodol bronchography These media have the property of clinging to the bronchial mucosa by capillary attraction in thin films and readily enter the alveoli when used in excessive amounts, or when of low viscosity Admixture of the basic suspension with Dionosil confirmed a parallel behaviour for this suspension From these considerations it is assumed that such media will remain *in situ* long enough to be phagocytized and otherwise distributed throughout the lobe

Retention of oily media in the lungs with anesthetized bronchi depends on the absence of the cough reflex and the suction action of inspiration which exceeds the expellent effort of expiration This phenomenon is constantly seen in bronchography when the oily contrast medium is seen to make jerky progress towards the periphery of the lung with each inspiration This inspiratory pull is quite forceful since it functions anti-gravitationally as can be seen when upper lobes fill when the catheter

is juxtaposed at an upper lobe orifice even when the patient is erect Bronchoscopically this retention is confirmed following introduction deep into a lobe, when prolonged waiting will not reveal the presence of the medium at the mouth of the orifice

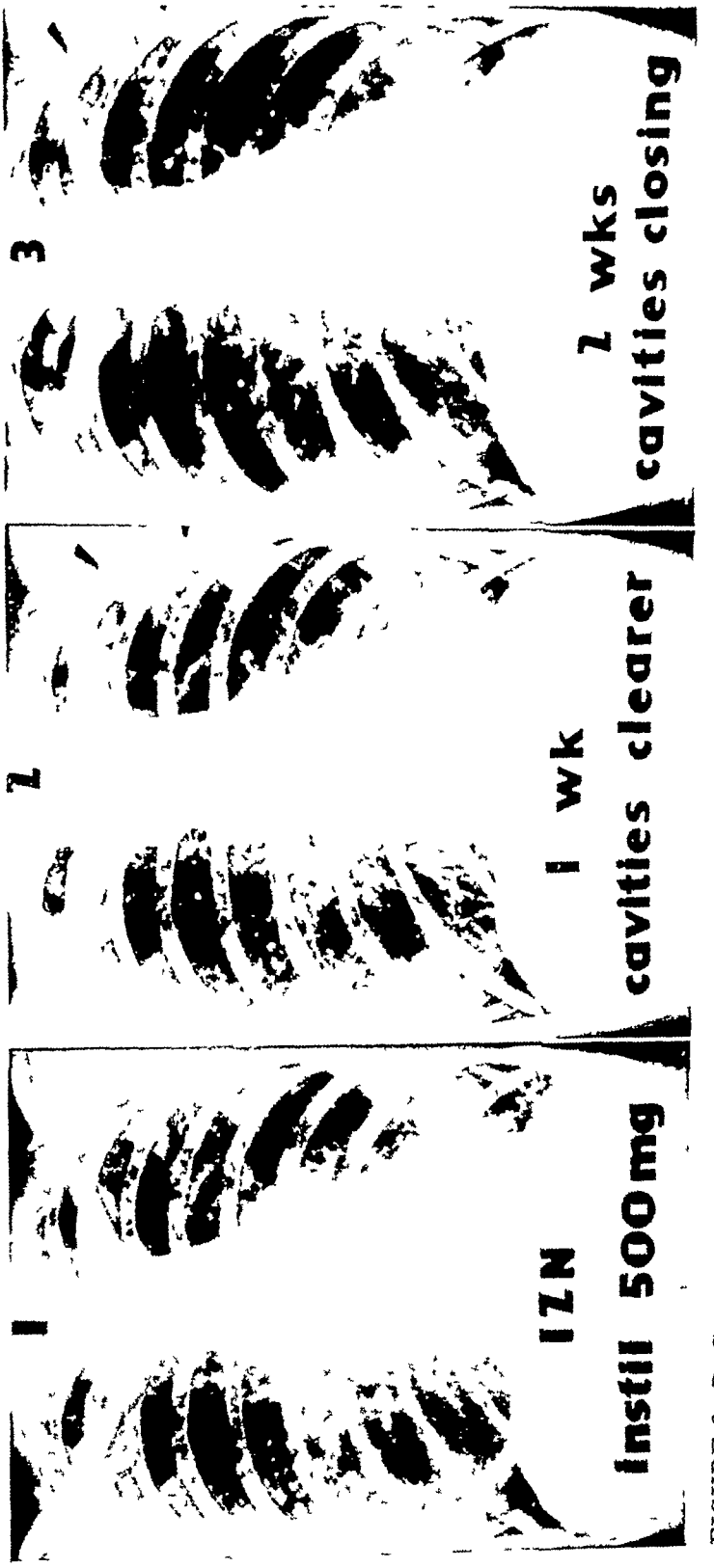


FIGURE 3 D S, a white female, age 23, with positive bronchial aspirate and far-advanced bilateral lesions of the infiltrative and cavitational types Patient acutely ill In the serial x-rays note the specific lytic action of the INH endobronchial instillations on the lesions and the rapid restoration to normal tissue in a matter of weeks (See view 4 & 5 on facing page)

Lipoid granulomas following the instillation of peanut oil based contrast media have been reported [15] Personal experience with similar media in 297 recorded five-lobe bronchograms and 70 penicillin (peanut oil base) [12] instillations would indicate, at least in the author's experience, that such incidence is comparatively rare None were encountered in the above cases In the present study 71 instillations were made with the basic suspension with no evidence of such granulomas An excellent opportunity was present to detect them since all patients had weekly chest films taken following instillation and later at monthly intervals throughout the period of observation In none of the series was there any indication of alien shadows which could be interpreted as granulomas

Toxic Manifestations of INH Suspension

Preliminary studies with the basic suspension indicated that this medium was well tolerated by the parenchyma as well as the host with the exception of a transient pneumonitis which occurred soon after the introduction into the lobe The typical reaction, as observed on x-ray film study, consisted of an over-all blurring when compared with the original film and a suggestion of a severe exudative process, which made one believe that the lesion had undergone a precipitous aggravation With the exception of a slight pyrexia systemic reactions or symptoms did not occur This process cleared rapidly within the space of one week but recurred following subsequent instillations though not to the same extent No permanent effect on the parenchyma was noted In the cases studied only one was considered severe, one moderately severe, and four slightly so In the others no appreciable change could be detected

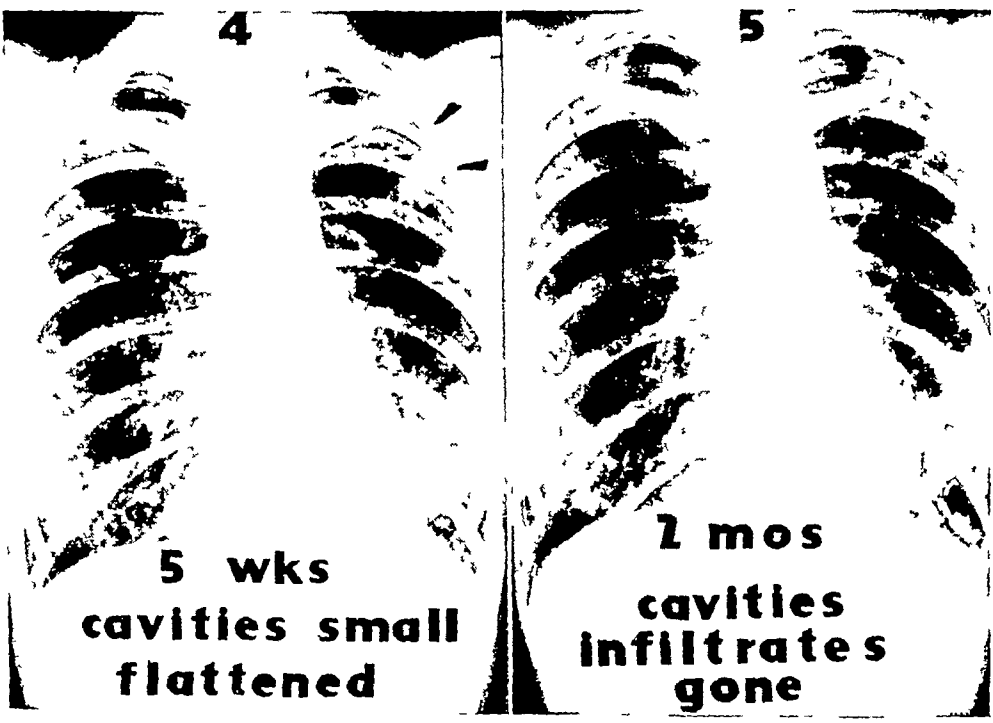


FIGURE 4 J S, a white male, age 45, with a negative bronchial aspirate and bilateral far-advanced fibrocaseous lesions with a large cavity in LUL History of recent sanatorium care for over 1 year on conventional therapy with INH, PAS, and SM In the serial x-rays note the rapid decrease in the size of the cavity following 1 INH instillation as well as the resolution of the associated infiltrates Cavity proper actually closed in 7 weeks (See view 4 & 5 on facing page)

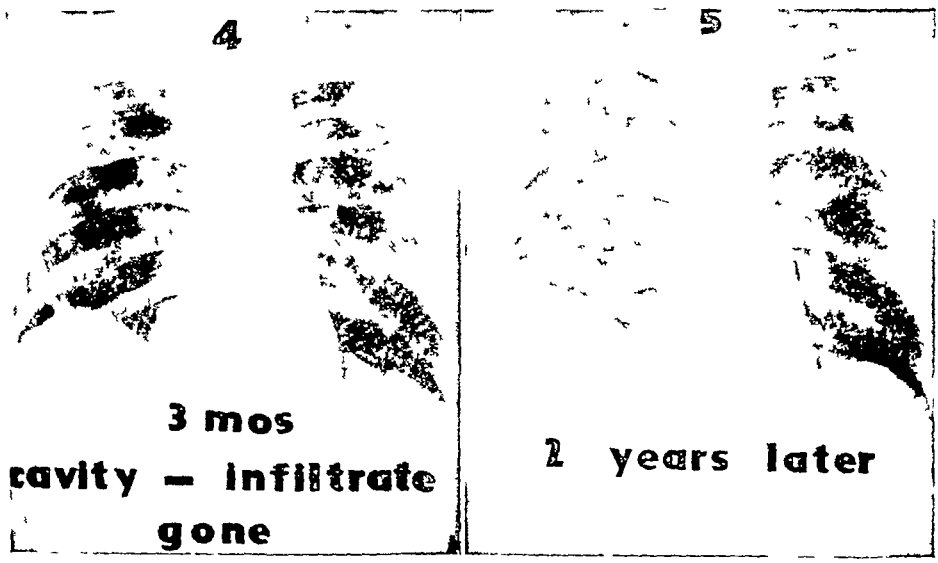
Clinical Material Used in the Study

The patients studied in this series were not selected but were treated as they appeared in sequence All were ambulatory and only the more severely ill were confined to bed until the acute symptoms had subsided, but in no case longer than two weeks They are classified on the basis of x-ray film findings and the severity of this involvement All but two were on concomitant oral INH with conventional dosages Two pregnancies, two diabetics and one far-advanced unilateral bronchiectasis were the non-tuberculous associated findings in the series Two had complicating pleural effusion In addition two had persistent cavities with pneumothorax failure One had tuberculous bronchostenosis of the left side with a destroyed lung Two were post-surgical positives—one a lobectomy with exudative spread and the other an ivalon sponge plombage The others ranged from acute exudative to the chronic fibro-caseous and fibroid types though in some these phases were combined Many cavities were encountered in the series—some single and others multiple in the same patient

Technique of Secretion Studies

It was decided for the purpose of this study to use a refinement of the standard technique for the detection of the tubercle bacillus This method yields a higher percentage of positives than is possible with the expectorate and reduces the number of false negatives It has been the author's impression for some years that the usual sputum and gastric search for tubercle bacilli is rather coarse, tedious, and prone to many false negatives, furthermore a positive expectorate usually connotes fairly advanced disease and waiting for such a finding may make us temporize in specific therapy

All the patients were bronchoscoped and the secretions obtained directly from the infected lobe or lobes by a special tubercle bacillus collector designed by the author [17] All initial aspirates were studied by smear,



culture, and guinea pig inoculation whenever possible and the same was done when a persistent negative smear was obtained The initial aspirate was generally sufficient for all three studies, though subsequent aspirates were found extremely scanty and frequently only a sufficient amount was obtained for a smear

Technique of Laryngotracheobronchial Anesthesia

Proper anesthesia is a *sine qua non* as without it the procedure becomes a waste of time and effort The cough reflex must be completely abolished not only in the involved bronchus but in all the others as well The author has devised a method of anesthesia for bronchoscopy and bronchography which is safe and effective for these purposes[18] and has been used in all the patients of this series Special attention must be paid in this technique, however, to spraying the trachea and lobar bronchi with an endobronchial atomizer prior to attempting the instillation of the basic suspension It is wise to spray these structures and then wait about five minutes before instilling If abundant secretions are present, it is necessary to completely aspirate the entire tracheobronchial tree as surface anesthesia is relatively ineffective in their presence

Various Methods and the Instruments Used for the Instillation of INH Oily Suspension in the Lung

1 *Instillation with the Standard Bronchoscope*

For instillation of the basic suspension into the lung bronchoscopically a new instrument had to be devised so that this could be done accurately and effectively Since most of the lesions existed in the upper lobes, a problem arose when the standard bronchoscope was used This instrument is generally best used for instillation purposes in the bronchial axis, when an ordinary metal catheter with a Luer-lok tip may be used The designing of a special catheter made possible upper lobe instillation with little difficulty This instrument consists of a monel tube of proper length whose tip was protected with a hollow ball and its terminal portion bent at an angle which was sufficient to permit passage through a 7 mm lumen Its proximal end was equipped with a Luer-lok adapter with a directional index bead in the plane of the curve With this equipment the bronchoscope is placed opposite the upper lobe to be instilled and the patient's head and neck rotated to the opposite direction The bronchoscope lip is then engaged in the lobar bronchus spur and the special catheter manipulated to enter the lobar bronchus which is now almost in the bronchoscopic axis Care must be taken that the catheter end is not placed into a segmental bronchus which may then be filled to the exclusion of other diseased segments This is particularly true of the anterior segment of the right upper and the lingular division of the left upper lobes In practice, it is sufficient to introduce the suspension only into the lobar orifice as it will automatically be aspirated into the various segments of the lobe if the respiratory physiology is not too impaired Accurate segmental localization is not necessary, except for

special reasons, since it is rather difficult to decide on x-ray observations alone how many segments are involved in a tuberculous process

2 *Instillation with Special Optical Catheterizing Bronchoscope (Pentascope)* (Fig 1)

A more accurate technique for instillation is with the use of an optical catheterizing bronchoscope designed by the author for this specific purpose With this instrument it is possible to instil accurately into any lobar orifice under direct vision and even into segmental bronchi

3 *Instillation by Bronchographic Technique*

To extend this study for the benefit of those skilled in bronchography a technique of instillation has been worked out by the addition of Dionosil to the basic suspension which renders its adequately radiopaque The

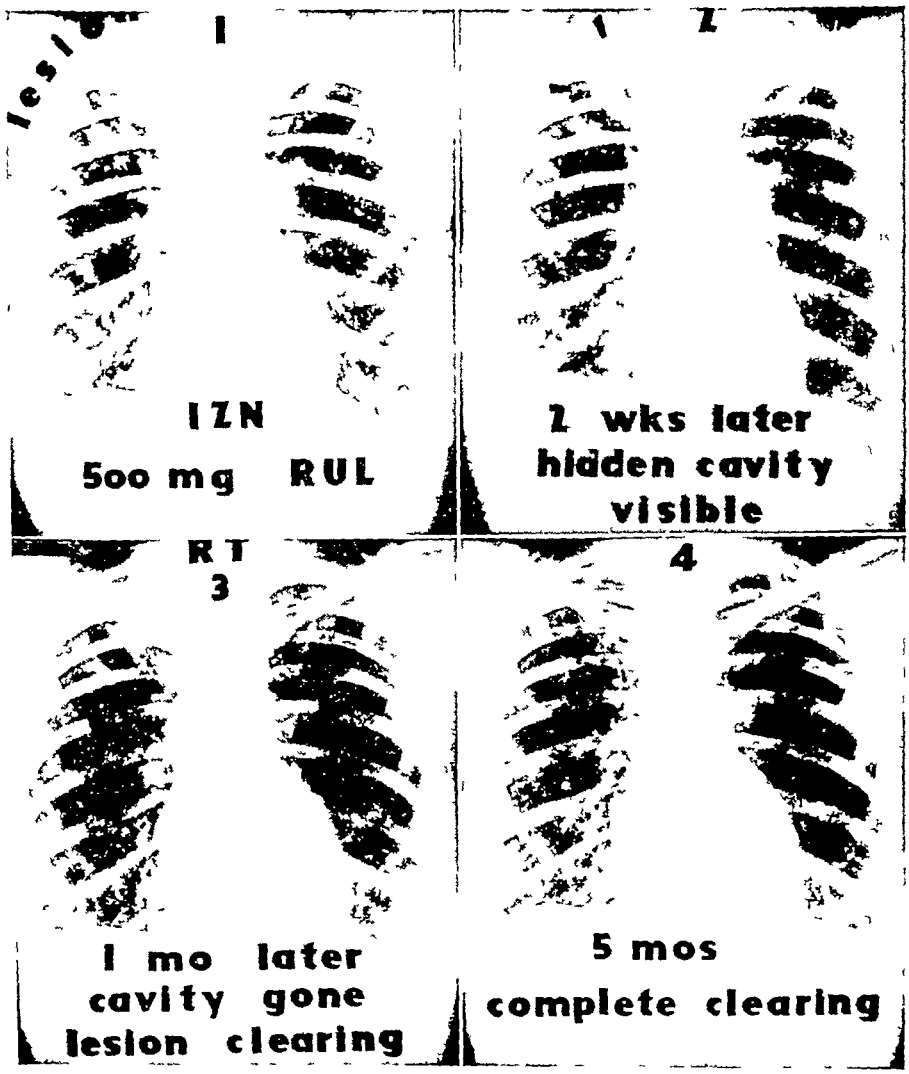


FIGURE 5 R T, a white female, age 31, with positive bronchial aspirate Note rapid clearing of the super-imposed tuberculous infiltrate revealing a hidden cavity The cavity closed and the lesion almost completely regressed in 1 month In 5 months there is complete clearing of the lesion with restoration to normal of parenchymal markings

author prefers a bronchoscopic approach even when using this modified suspension for reasons of proper diagnosis, detection of obstructive or stenotic lesions, proper aspiration and adequate surface anesthesia, as well as for the progress detection of tubercle bacilli in the aspirate The bronchographic catheter is introduced through the bronchoscope to the side desired and the latter withdrawn leaving the catheter in place The catheter used for this purpose is a standard 12 F woven ureteral catheter, non-graduated, non-x-ray (C R Bard, Inc, Summit, New Jersey) (No 302), which has been modified by the insertion of a snugly fitting two inch monel tube in the tip so that it occludes the second orifice The tip over the metal tube is bent at an angle which still permits passage through a 7 mm lumen bronchoscope The proximal end was equipped with a special Luer-lok adapter and small tubular insert which prevents closure of the lumen when the adapter is tightened over a plastic or rubber tubular sleeve The original length of the catheter is adequate for working over a fluoroscopic screen and the terminal curve and single aperture permit accurate localization of the suspension within the lobar orifice to be filled Simple rotation at the carina permits easy shift from one main stem bronchus to the other The terminal metal insert renders the tip constantly visible during fluoroscopy

Lately it has been found advantageous to use the radiopaque suspension with all of the above techniques since hidden cavities and bronchiectatic areas become visible and obviate the use of tomography An excellent film record can be obtained for verification of the degree and extent of filling Another innovation has been the routine complete filling of all five lobes at the same sitting after the known diseased lobes have been filled This takes care of latent or non-detectable infection in the other lobes and to date has not been found harmful

No matter which of the above techniques is used instillation should be gentle, deliberate and slow Most of the lobes will usually tolerate 10 ccs of the suspension It must be remembered that aspiration into the branch bronchi from the lobar bronchus takes some time and that flooding of the lobar bronchus too quickly will evoke a cough reflex no matter how adequate has been the surface anesthesia The phenomenon may be explained by the pressure of air retained in the bronchioles and alveoli eliciting a distension cough reflex not controlled by the anesthesia

Positioning of the Patient for Instillation

For bronchoscopic techniques instillation is originally made with the patient in the standard bronchoscopic position though immediately following this the patient is placed in more advantageous positions to take advantage of gravitational forces

For upper lobe work the patient is placed in an oblique position with the side filled downward and the table inclined 5 or more degrees cephalad for about 15-20 minutes For middle lobe the position is face down with the table in the horizontal position For lower and lingular branch instillations the patient lies on his back with the table tilted 5 degrees

caudad The Rittei electiic hydiaulic table with the modified head iest is excellent foi these puiposes as well as foi geneial endoscopic woik Following the 15-20 minute iest, the patient is iemoved to bed oi couch and the same positiion duplicated except foi tilting He is admonished not to cough Foi multiple lobe filling a compiomise positiion is aiianged so that the flow will giavitate to the lobes filled Foi example, when both uppei lobes have been instilled the most favorable positiion will be flat on the back with the table tilted cephalad

Foi five lobe filling with the bi onchogiaphic technique the patient lies on the iadiogiaphic table on his back The moie involved lobe oi lobes aie filled fiist by piopei postuial techniques Oblique positioning to the iight oi left will almost completely fill the tiacheobronchial tiee of any paiticulai side though a cephalad tilt while the patient is in this oblique positiion will take caie of the upper lobes The middle lobe fills best and spontaneously with the patient face downwaid with the table in the hoiizontal positiion A good piocedure to follow is to fill first the upper lobe with a tilt, the lowei lobe with the table hoiizontal oi tilted caudad The same is then done with the othei side The patient is then placed on his face foi automatic filling of the middle lobe Expeiience will acquaint the opeiatoi with the time inteivals needed for each side Following instillation the patient iests on the iadiographic table foi 15-20 minutes piioi to iemoval to bed oi *cough* It has been noted that once the suspensiion has penetiated the bi onchioles and alveoli it iemains there even aftei the cough ieflex ietuins, though the patient still is exhorted not to cough

Results

The iesults obtained in this study are summaiized in Tables I, II and III With iespect to conveisiion, 86 per cent of the patients became and stayed negative duiing the peiiod of observation The shortest inteival was 21 days and the longest 11 months These figures, however, are not too accurate since the conversiion inteival was determined fiom the first positive to the fiist persistent negative, though in many cases bi onchoscopic aspiiation was not done until some time after the lesions had cleaied or became stationary The actual conveisiion time could have been much shoitei The aveiage peiiod of tabulated conversiion was 96 days

TABLE I
CONVERSION STUDIES WITH ENDOBRONCHIAL INH

No Cases	18
No Positive	14 (78 pei cent)
Aveiage Instil /pnt	4 (500 mg each)
No Converted	12 (86 per cent)
Aveiage Time foi Conveisiion	96 (days)
Failuies Lobect, Plombage	2 (14 per cent)

TABLE II
X-RAY CHANGES FOLLOWING INH ENDOBRONCHIAL INSTILLATION

No Cases	18
Average Instil /pnt	4 (500 mg each)
Complete Clearing	10 (59 per cent)
Exudate Clearing	14 (100 per cent)
Cavity Closure	10 (100 per cent)
Time to Clear/Close	55 days average
Time Remaining Static	14 months average
No Change 2 Fibroid, 1 Plombage 1 Destroyed Lung	4 (22 2 per cent)

The x-ray film findings were rather striking with complete clearing of visible lesions in 10 of the series and complete closure in 10 separate patients with cavitation Closure was effected in cases of single as well as multiple cavities The time for clearing of the lesions as well as closure of the cavities was also remarkable with the shortest interval 14 days and the longest 120 days with an over-all average of 55 days Complete clearing of the lesions was noted in 59 per cent of the series

Weight gain varied from two to 29 lbs The two diabetics, however, because of their dietary regimen lost six and 10 lbs Two patients neither gained nor lost With these exceptions the average weight gain distributed amongst the remaining 14 patients was 13 lbs

The maximum sedimentation rate (MSR, Cutler technique) was usually proportional to the rate of clearing and systemic improvement The greatest drop, prior to treatment, was 15 mm and the lowest 0 5 mm with the average of 6 0 mm Following treatment the highest was 7 0 mm (bronchiectatic case) and the lowest 0 5 mm with an average of 2 2 mm

An attempt was made to compare the findings in this pilot experiment with the gross results as obtained from a compilation of the figures found in the literature (Table III) Comparison is of course only relative because of the small number of cases in this pilot experiment It will be noted

TABLE III
RESULTS OF PILOT STUDY COMPARED WITH AVERAGES IN THE LITERATURE*

	Literature Per Cent	Pilot Study Per Cent
Conversion	48	86
Gen x-ray improv	60	82 5
Exudate Clearing	24	100
Cavity Closure	30	100

*References 1 to 5

that the conversion rate is rather high (86 per cent), the x-ray improvement moderately higher (82 5 per cent), and the clearing of the exudates and cavity closure 100 per cent

Discussion

It would seem from the results obtained in this pilot study that the theoretical considerations which made it possible were justified Apparently the airways may be safely used as a portal of therapy with antituberculous agents in oily suspension and that the *concept of lobar or multilobar rather than body saturation* is a feasibility It is also evident that to be effective the lobar physiology must not be too grossly impaired With this type of therapy as well as with all others the need for early detection is still in order

It is important to note the specific lytic action of the suspension on the tuberculous foci as seen on the serial x-ray films with the tendency to restoration to normal of the parenchyma The onset of a transient INH pneumonitis should not be interpreted as an aggravation or failure of the procedure as following the apparent exacerbation, the foci begin to clear with disappearance of the exudates, visualization of hidden cavities, and reappearance of the parenchymal components Cavity walls become better defined, thinner and the cavity itself soon becomes distorted or collapsed due to external pressure on its weakened walls, or it may diminish in size weekly with eventual complete closure In the series complete disappearance of good-sized cavities usually occurred in six to seven weeks

A question may arise on the relative value of the endobronchial therapy *per se* since it was combined with oral therapy of INH and PAS in many of the patients An attempt was made originally to confine the therapy only to the endobronchial instillation and this was actually done in two of the patients by mutual consent, the others insisted in adjuvant therapy once the diagnosis of tuberculosis was made These two patients (CS and JM) had excellent response with the endobronchial medication and cleared completely with only one instillation One (J S) had been in a sanatorium for over one year on full doses of INH, PAS, and SM with a persistent large cavity One endobronchial instillation closed the cavity in seven weeks Several others of the series had complete regression of the lesions following a first instillation but had cavitational recurrences in different locations in spite of the fact that they were on continuous oral medication in full doses A second instillation promptly resolved the lesions and there has been no further recurrence Apparently oral medication in these particular patients was not effective in controlling or preventing recurrences of lesions

From these observations it may be stated that the endobronchial therapy for pulmonary tuberculosis is indeed specific and apparently independent in its action from any effect of oral therapy

The rapid disappearance of fluid in the two cases of effusion complicating the pulmonary lesions would indicate that this treatment is also effective against tuberculous effusions Bronchoscopic observations with

respect to secretions show that these are considerably reduced in quantity and modified in character following INH instillation, and in many of the patients stopped completely within a short interval Papanicoloau smears showed a rapid disappearance of the leukocytes with reversion to a normal cytogram

Dosage schedules, because of the pilot nature of this study were more or less arbitrary and instillations were generally repeated when it was considered that an additional instillation would further effect the regression of the lesion For the same reason accurate spacing could not be determined since the time intervals of effective change and quantitative response of the lesion were unknown factors In general, it would now seem that from one to four instillations are necessary for maximum therapeutic effect spaced at 20 day intervals This arrangement, however, is a mere guide and, if the lesions persist or recur, a second instillation is in order at any particular time

The amount of the suspension used was generally 10 cc per lobe and for these purposes the lingular division is considered as a separate lobe Multiple instillations, when indicated, are made at the same time With the five lobe bronchographic technique as much as 25-30 cc of the radiopaque suspension may be used

Resistance of the tubercle bacillus as judged clinically has not been a factor in this study when using the endobronchial instillation, though it may be expected when the scope of this technique is enlarged to a greater number of cases

NOTES

The INH preparation used in this series was the "Lyophilized Isoniazid 'Panray,'" which was kindly supplied for this study by the Panray Corporation, New York, New York

All the bronchoscopic instruments mentioned as well as the optical catheterizing bronchoscope (Pentascope) and the special catheters are presently being manufactured by the George P Pilling and Sons Company, Philadelphia, Pennsylvania, to whom the author has given originals which were personally designed and made

SUMMARY

1 A series of 18 cases of pulmonary tuberculosis of various types and degrees of severity has been treated by the endobronchial instillation of an oily suspension of isonicotinic acid hydrazide as a pilot experiment

2 This study would indicate that, with this new portal of therapy

a The conversion rate becomes high and is obtained in rather short intervals

b Complete disappearance of the lesion, its improvement and cavity closure incidence is higher and shorter in time intervals than with conventional oral therapy alone

c INH in oily suspension endobronchially introduced has a pronounced specific lytic action on tuberculous foci

3 The medication and the techniques described are safe and free from any detrimental parenchyma or constitutional effects

4 The clinical and roentgen results appear to be permanent and not of short duration

5 *Lobar or multilobar drug saturation* is proposed as a new concept in the chemotherapy of pulmonary tuberculosis

RESUMEN

1 Como un experimento piloto, 18 casos de tuberculosis pulmonar en varias formas, se han tratado con instilaciones de una suspensión aceitosa de hidrazida del ácido isonicotínico

2 El estudio indicaría

a La proporción de conversiones se hace elevada y es obtenida a corto plazo

b La desaparición completa de la lesión, su mejoría y el cierre de cavidades es más elevada y se obtiene más pronto que el método oral

c INH (isoniacida liofilizada) en suspensión oleosa endobronquialmente tiene una acción lítica pronunciada en los focos tuberculosos

3 La medicación y la técnica descritas son seguras e incapaces de dañar el parénquima y de causar daños al estado general

4 Los resultados clínicos y radiológicos parecen ser permanentes y no de corta duración

5 *La saturación lobar o multilobar* se propone como un concepto nuevo en la quimioterapia de la tuberculosis

RESUME

1 A titre d'essai expérimental, une serie de 18 cas de tuberculose pulmonaire de type et de gravités différentes a été traitée par instillation endobronchique d'une suspension huileuse d'hydrazide d'acide isonicotinique

2 Cette étude indiquerait que, avec ce nouveau mode de traitement

a) le taux de négativation est élevé, et est obtenu en un temps relativement court,

b) la disparition complète de la lesion, son amelioration et la fréquence de la fermeture cavitaire est plus élevée et survient dans un intervalle de temps plus court qu'avec le seul traitement buccal conventionnel

c) L'INH (isoniazide lyophilise) en suspension huileuse administré par voie endobronchique a une action lytique spécifique prononcee sur les foyers tuberculeux

3 La médication et les techniques decrites sont sans effets secondaires nocifs sur le parenchyme ou sur l'état général

4 Les résultats cliniques et radiologiques semblent être stables et de longue durée

5 *La saturation medicamenteuse lobaire ou multilobaire* est proposée comme un nouveau procédé de la chimiothérapie de la tuberculose pulmonaire

ZUSAMMENFASSUNG

1 Eine Reihe von 18 Fallen von Lungentuberkulose verschiedener Formen und Schweregrade wurde in einem Routineversuch mit endobronchialer Instillation einer oligen Aufschwemmung von INH behandelt

2 Diese Untersuchung vermag zu zeigen, dass mit diesem neuen Zugang der Therapie:

a. Die Ziffer der Bazillenfreiheit gross und in ziemlich kurzem Zeitabschnitt erreicht wird

2 Komplettes Verschwinden der Herde, ihre Besserung und das Vorkommen von Kavernenverschluss ist haufiger und erfolgt in kurzeren Zeitraumen als durch die ubliche orale Therapie allein

b INH (lyophilisiertes INH) in oliger Aufschwemmung endobronchial eingefuhrt hat eine ausgepochene Lytische Wirkung auf tuberkulose Herde

3 Die beschriebene Verordnungsweise und Technik ist sicher und frei von irgendwelchen schadlichen Wirkungen auf Parenchym oder Konstitution.

4 Die klinischen und röntgenologischen Resultate scheinen anhaltend und nicht von kurzer Dauer zu sein

5 Lobare oder multilobare Arzneimittelsattigung wird als ein neuer Begriff in der Chemotherapie der Lungentuberkulose vorgeschlagen

REFERENCES

1 Silikoff, I J and Robitzek, E H "Tuberculous Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid," *Dis Chest*, 21 385, 1952

2 Robitzek, E H, Selikoff, I J, Mamlok, E and Tendlau, A "Isoniazid and Its Isopropyl Derivative in the Therapy of Tuberculosis in Humans Comparative Therapeutic and Toxicological Properties," *Dis Chest*, 22 1, 1953

3 United States Public Health Service, Federal Security Agency "Control Study of Comparative Efficiency of Isoniazid, SM-Isoniazid and SM-PAS in Pulmonary Tuberculosis Therapy," *Am Rev Tuberc*, 67 108, 1953

4 Salkin, D and Schwartz, J A "Roentgenological Changes of the Lung Associated with Isoniazid Therapy in Pulmonary Tuberculosis," *Dis Chest*, 26 255, 1954

5 Dooneief, A S and Hite, K E "Indefinitely Prolonged Chemotherapy for Tuberculosis," *Am Rev Tuberc*, 70 219, 1954

6 Bormioli, R "Resultats de la Therapie Endo-bronchique avec L' I A I dans Quelques Cas Particuliers de T B C Pulmonaire Specifiquement Cavereuse," Transactions II International Congress of Bronchoesophagology, p 150, 1953

7 Bonarrigo, N "Bronchoscopy, Bronchoscopo-therapy, Bronchoscopic Aspiration and Endobronchial Instillations of Antibiotics in Pulmonary and Bronchial Tuberculosis," Transactions I International Congress of Bronchoesophagology, p 73, 1952

8 Sweany, H C and Dunbar, F P "The Problem of Bacterial Resistance in Antimicrobial Therapy of Tuberculosis," *Dis Chest*, 27 260, 1955

9 Lemon, W S "The Anatomical Factors Involved and the Mechanisms Employed in Removal of Minute Particles of Foreign Material from the Lungs An Experimental Study," *Transactions of Assoc Am Phys*, 53 278, 1937

10 Machaness, G B and Smith, N "The Action of Isonicotinic Acid Hydrazide on Intracellular Tubercle Bacilli," *Am Rev, Tuberc*, 66 125, 1952

11 Machaness, G B and Smith, N "The Bacteriocidal Action of Isoniazide, Streptomycin, and Terramycin on Extracellular and Intracellular Tubercle Bacilli," *Am Rev Tuberc*, 67 322, 1953

12 Carabelli, A A "Acute Bronchopulmonary Suppuration Therapy with Endoscopic Application of Oleaginous Penicillin," *Dis Chest*, 25 316, 1954

13 Miller, W S "The Lung," Charles C Thomas, Baltimore, p 3, 1937

14 Porcellati, G and Prezioni, P "Biological Transformation of Isonicotinic Acid Hydrazide," *Enzimologia*, 17 47, 1954 *Am Rev Tuberc* (Abstracts), 73 64, 1956

15 Storis, R P, McDonald, J R and Good, C A "Lipoid Granuloma of the Lung following Bronchography with Iodized Oil," *J Thoracic Surg*, 18 561, 1949

16 Sullivan, R D, Barclay, R K and Karnofsky, D A "Effects of High Doses of Isoniazid in Man," *Am Rev Tuberc*, 69 957, 1954

17 Carabelli, A A "Endoscopic Collection of Neoplastic Cells and Tubercle Bacilli from the Bronchi," *Dis Chest*, 18 98, 1950

18 Carabelli, A A "The Use of Pontocaine in Subposological Quantities for Bronchoscopy and Bronchography," *Anesthesiology*, 13 169, 1952

SECTION ON CARDIOVASCULAR DISEASES

Patent Ductus Arteriosus in the Adult With Partial Reversal of Flow

PAUL WINCHELL, M D , JAMES REDINGTON, M D
and RICHARD L VARCO, M D , F C C P*
Minneapolis, Minnesota

The clinical and physiological characteristics of the uncomplicated patent ductus arteriosus in the adult have been well-defined and understood for many years A typical continuous murmur usually develops early in life, the electrocardiogram is usually normal or shows a left axis deviation, and heart fluoroscopy ordinarily shows only mild to moderate left ventricular enlargement, vigorous aortic pulsation, and increased pulmonary blood flow In addition, cyanosis does not occur unless severe congestive cardiac failure develops in the terminal stages of the disease [1]

In 1925, following a review of 16 atypical cases of patent ductus arteriosus in which right ventricular hypertrophy was present, it was pointed out that reversal of flow through the ductus arteriosus and the consequent development of lower extremity cyanosis and clubbing could and probably did occur in at least six of the patients studied [2] Recently the syndrome of patent ductus arteriosus with pulmonary hypertension and reversal of flow through the ductus arteriosus has been well-described and documented in scattered reports [3-6] The following cases are believed representative of that group

Case Reports

Case 1 M C , a 44 year old white woman entered the hospital for the first time on December 30, 1953 She gave a life-long history of dyspnea on effort and of becoming tired easily As a child she had been "sickly" and never able to keep up with her playmates Cyanosis on exertion was first noted in 1940 at the age of 30 Hemoptysis of approximately one-half cup of blood first occurred in 1947 and was subsequently followed by eight similar episodes over a period of four years She had previously worked as a beauty shop operator but after 1946 was limited to manicure work because of weakness and dyspnea There was no history of dyspnea at rest or of orthopnea She noted hoarseness on several occasions

She had been studied in hospitals for the first time in 1951 when she complained of severe dyspnea on exertion and could not walk over 20 feet without stopping to rest On examination in 1951, she was noted to have cyanosis of the lips and fingers and marked cyanosis with definite clubbing of the toes The blood pressure was right arm 108/92, left arm 112/90, right leg 140/94, and left leg 142/90 mm Hg The lungs were clear The heart was generally enlarged The pulmonary second sound was louder than the aortic second sound A low-pitched diastolic murmur was heard in the fourth inter-

*From the Departments of Medicine and Surgery, University of Minnesota Medical School, University Hospitals

TABLE I
CATHETERIZATION DATA—1953—CASE 1

Site of Blood Sample	Pressure Mm Hg	O_2 Content Vol Per Cent	O_2 Saturation Per Cent
Pulmonary artery	85/60	18 4	63
Right atrium		18 0	62
Femoral artery	110/89	17 6	60
Brachial artery (left)	117/88	27 6	94

The pulmonary artery and systemic artery pressures were not recorded simultaneously, which may account for the considerable difference between them

costal space to the left of the sternum There was no peripheral edema The hemoglobin was 21 1 gm /100 ml, the venous pressure 7 0 cm of Na citrate solution The arm to tongue circulation time (decholin) was 36 seconds while the vital capacity was 88 per cent of normal An electrocardiogram showed right axis deviation and right ventricular strain Cardiac fluoroscopy showed considerable enlargement of the right ventricle and less marked enlargement of the left ventricle The findings at cardiac catheterization are recorded on Table I She was discharged with a probable diagnosis of Eisenmenger's complex

During the next two and one-half years, she worked 15 to 30 hours weekly until late in 1953 when she re-entered the hospital because of increasing fatigue and dyspnea On examination she was found to be a malnourished, chronically ill 44 year old woman with severe dyspnea on effort The blood pressure was 100/60 mm Hg There was marked cyanosis and marked clubbing of the toes (Figure 1) The lungs were clear The heart was generally enlarged with a diffuse maximal impulse over the fourth intercostal space to the left of the sternum The pulmonary second sound was accentuated A grade II blowing diastolic murmur was heard along the left sternal border radiating to the apex when the patient was in the left lateral decubitus position A rough systolic murmur was heard intermittently at the base There was no peripheral edema The hemoglobin was 23 3 gm /100 ml Electrocardiogram showed right ventricular preponderance and strain (Figure 2) Chest x-ray film (Figure 3)

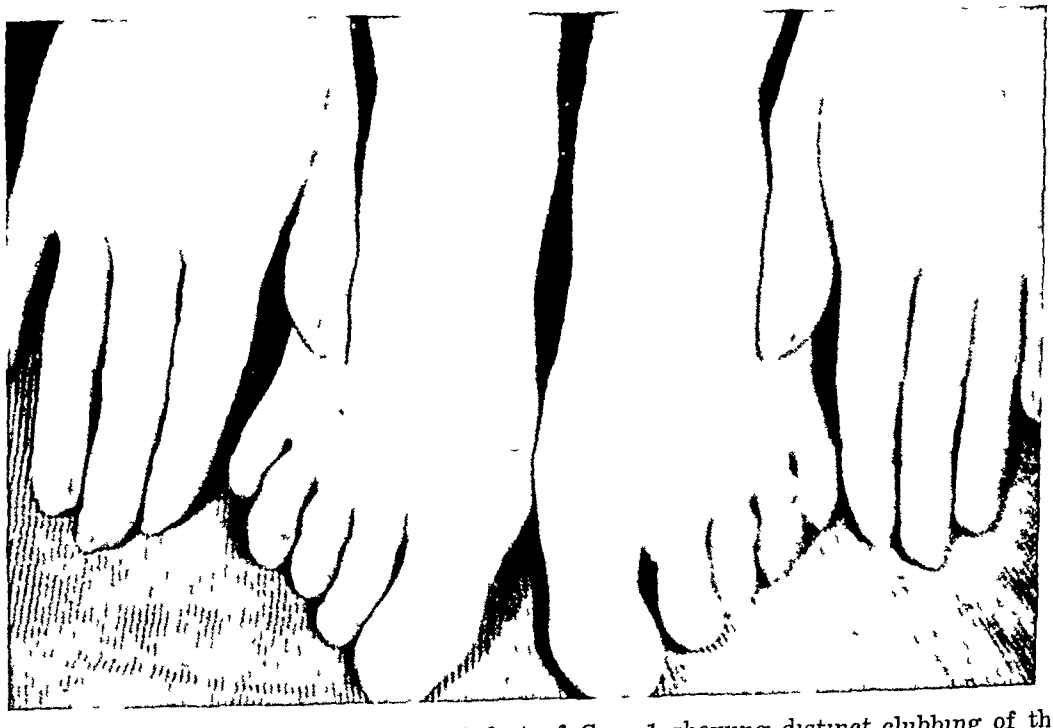


FIGURE 1 Photograph of hands and feet of Case 1 showing distinct clubbing of the toes without similar changes in the fingers

TABLE II
EFFECTS OF BREATHING 100 PER CENT O_2 ON FEMORAL ARTERY SATURATION—CASE 1

	1951	1953
	Per Cent	Per Cent
Femoral saturation at rest	53	60
Femoral saturation after breathing 100 per cent O_2	74	69

In 1951 there was a considerable drop in the amount of desaturated pulmonary artery blood shunting into the aorta after breathing 100 per cent oxygen Much less change was produced two years later under the same circumstances suggesting that the pulmonary resistance was less altered by high oxygen tensions in the inspired air

and cardiac fluoroscopy showed primarily right ventricular enlargement The pulmonary arteries were enlarged but the peripheral pulmonary vessels were diminished in size Arterial oxygen studies are recorded in Table II A retrograde aortogram through the left brachial artery outlined the aorta with no evidence of coarctation A slight outpocketing of the medial portion of the arch in the position where a ductus arteriosus is usually found was seen but there was no flow of dye from the aorta to the pulmonary artery As a result of the studies it seemed likely that the patient had

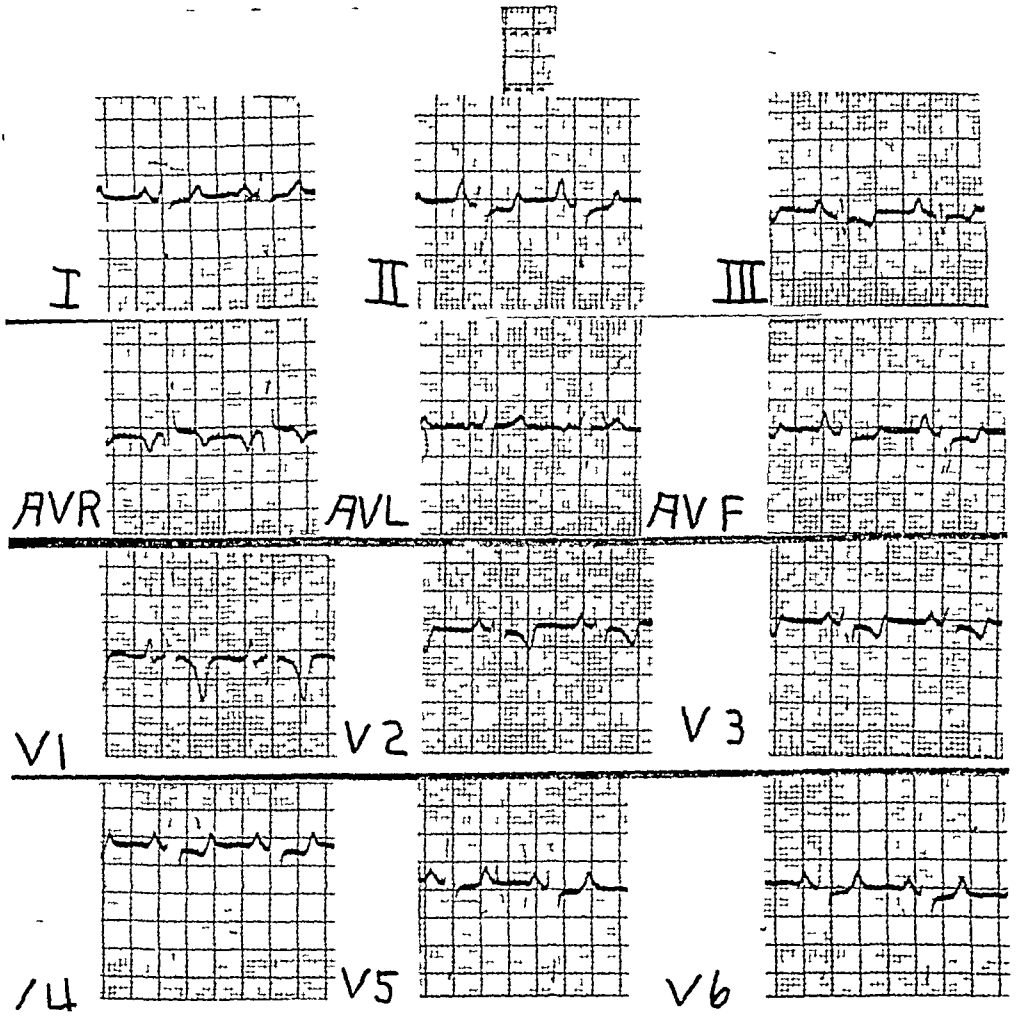


FIGURE 2 Electrocardiogram from Case 1, interpreted as showing marked right ventricular hypertrophy and strain, normal sinus rhythm

FIGURE 3 Posteroanterior and right-anterior oblique chest views of Case 1 Calcification in the ductus arteriosus is visible

a patent ductus arteriosus with severe pulmonary hypertension and a shunt from pulmonary artery to the distal aorta, with no other apparent cardiac defects

The seriousness of an operation was stressed for this patient However, she desired to undergo any type of corrective surgery which might benefit her While in the hospital she was a total invalid because of exertional dyspnea The plan was to place a small diameter shunt between the pulmonary artery and the left atrium before cross clamping the ductus arteriosus Then if the patient tolerated closure of the ductus

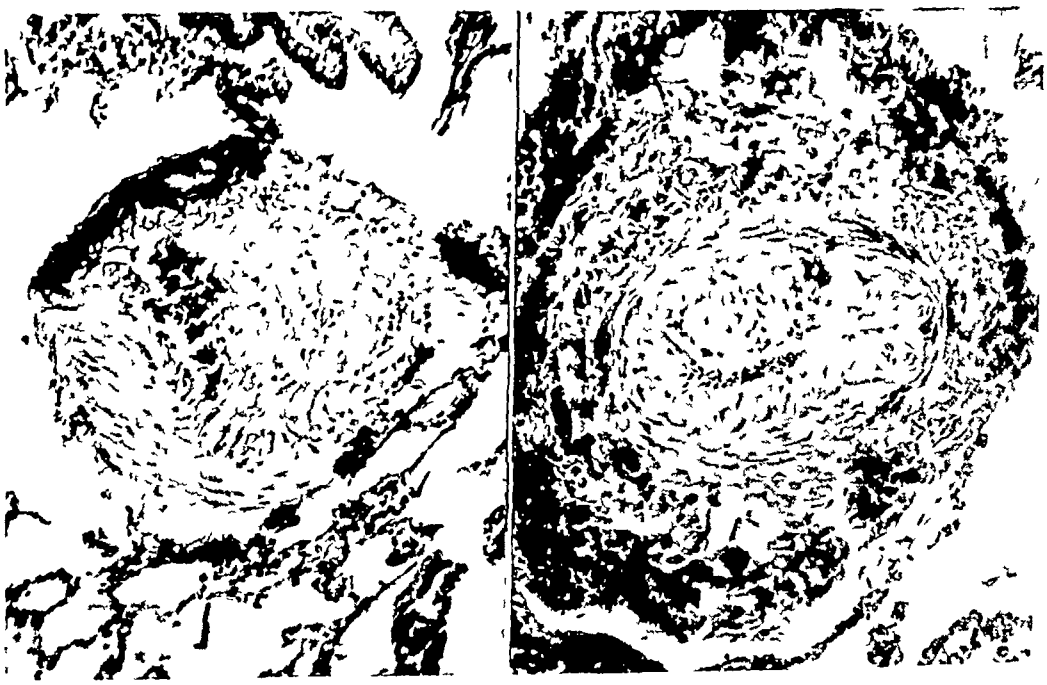


FIGURE 4 FIGURE 5

Figures 4 and *5* Photomicrographs of small pulmonary arteries from Case Striking intimal proliferation is present

arteriosus it was to be divided and ligated It was thought that this technique would decrease right heart work by decompressing any intolerable right ventricular pressures developing after the shunt through the ductus arteriosus had been eliminated Moreover, it was hoped that this leak would contribute a volume flow adequate to sustain sufficient blood volume in the systemic circulation, especially the coronary arteries during an interval when the right heart was incapable of pumping enough blood through the arteriosclerotic pulmonary circuit Perhaps with time for readjustment a regression of the lung lesions would follow Once her clinical status had improved enough, at a second operation the arterial shunt between the pulmonary artery and the left atrium could then be disconnected It was appreciated that such an anastomosis would result in mild generalized cyanosis rather than the regional cyanosis already present

At operation the ductus arteriosus was estimated to have a diameter of 20 to 25 mm It was thickened and contained calcium There were evident thrombi in all branches of the right pulmonary artery with wide spread calcific deposits in the arterial wall The proposed anastomosis of the left atrium to a branch of the pulmonary artery could not be carried out because of thromboses throughout the smaller pulmonary arteries A tentative clamping of the ductus arteriosus was attempted to note the heart's tolerance of the altered hemodynamics The cross clamping unfortunately eventuated promptly in ventricular fibrillation A normal rhythm could not be reestablished despite recourse to a variety of resuscitative techniques

At autopsy two areas of infarction were present in the upper lobe of the right lung The right and left pulmonary artery branches were dilated and showed a marked degree of atherosclerosis A laminated thrombus was present at the bifurcation of the right pulmonary artery and extended into the main lobar branches with complete occlusion of the opening to the upper lobe The ductus arteriosus entered the aorta 2 cm beyond the left subclavian ostium The aorta in this area showed moderate atherosclerosis and was calcified The left pulmonary artery was markedly atherosclerotic with calcification and sclerosis of the intimal layer Marked plaque formation and ulceration of the intima were present in the left pulmonary artery where the ductus arteriosus entered The right ventricle was hypertrophied and dilated, its walls measuring 1 2 cm in thickness The left ventricle measured 1 4 cm in thickness The valves were all normal No other cardiac defect was present

Microscopic examination of the lungs showed areas of atelectasis and infarction The smaller pulmonary arteries showed striking changes, mainly of thickening due to intimal fibrosis with fragmentation and duplication of the elastic fibers (Figures 4 and 5) Vascular lesions in the form of small cavernous channels supported by connective

FIGURE 6 Chest views of Case 2 Enlargement of both ventricles and the pulmonary artery segment is present

TABLE III
CARDIAC CATHETERIZATION DATA—CASE 2

Chamber	Pressure Mm Hg	O_2 Content Vol Per Cent	O_2 Saturation Per Cent
PA	102/64	17 54	83
RV	100/ 7	13 21	63
RA	6	12 98	62
SVC		12 79	62
IVC		13 01	62
FA		19 66	92

tissue containing endothelial cells were present Sections of the right pulmonary artery showed severe atherosclerotic changes with calcification as well as a laminated thrombus

Case 2 This patient was a 21 year old woman who gave a history of life-long inability to keep up with other people of her age Her symptoms were primarily those of shortness of breath on effort In addition, she had noted paroxysmal nocturnal dyspnea and ankle edema She had never been cyanotic Because of her cardiac symptoms she had been forced to discontinue school at an early age There had been many episodes of respiratory tract infection and bronchitis There was no antecedent history of rheumatic fever

The physical examination at the time of her first hospital admission was negative except for the heart and for a palpable thyroid gland adenoma, which with her hyperactivity and a fine tremor led to the clinical diagnosis of thyrotoxicosis The heart was not enlarged on physical examination There was a grade III systolic murmur heard best along the left sternal border and at the apex In addition, a grade I diastolic blowing murmur could be heard along the left sternal border There was no cyanosis of either the mucus membranes, the fingers nails, or the toe nails The blood pressure was 118/74 mm Hg

The pertinent laboratory findings on the first hospital admission were as follows The urine was within normal limits The hemoglobin was 15 3 gms and the white blood count was 6,600 with 49 per cent neutrophils, 42 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils, and 1 per cent basophil The radioactive iodine uptake was 53 per cent of the administered dose at the end of 24 hours An electrocardiogram showed atrial fibrillation at a slow rate The frontal plane axis was about +80° There were marked ST segment and T wave changes in leads II, III, AVF, and V5 and V6 suggestive of digitalis effect or possibly a left ventricular strain pattern No evidence of right ventricular hypertrophy could be seen Cardiac fluoroscopy showed marked enlargement of the heart which was thought to involve both the left and right ventricles Mild left atrial enlargement was also observed in the left anterior oblique view The pulmonary artery segment and the central and peripheral pulmonary arterial branches were considerably enlarged The aorta was thought to be small (Figure 6) The findings were consistent with a left to right shunt and because of the slight but definite left atrial enlargement it was thought that either a ventricular septal defect or a patent ductus arteriosus would be the more likely possibility

Cardiac catheterization was carried out and the significant findings are indicated in Table III Despite severe pulmonary hypertension a considerable left to right shunt at the level of the pulmonary artery was found and was thought to be consistent with either patent ductus arteriosus or an aortic pulmonic window

In view of the co-existing thyrotoxicosis it was thought advisable to control this portion of her illness first Initial attempts using propylthiouracil were not effective and it was necessary eventually to administer relatively large doses of radioactive iodine By February of 1956 she was somewhat hypothyroid, the radioactive iodine uptake being 6 6 per cent at 24 hours

She was readmitted to hospital in February of 1956 for an attempt at corrective surgery There had been little change in her symptomatology except that she had noted cyanosis with exercise on several different occasions Her symptoms of nervousness were well controlled and her other symptoms directly referable to the cardiovascular system were unchanged despite the fact that she was then hypothyroid

The physical examination at the time of her last admission showed the blood pressure to be 100/78 mm Hg The cardiac murmurs were unchanged It was thought that distinct but mild cyanosis of the nail beds was present

There were no significant changes in the laboratory studies other than in the arterial saturation A femoral artery blood sample collected at rest showed the oxygen saturation to be only 83 per cent In view of this finding simultaneous samples were taken from the right brachial artery and the left femoral artery in which the arterial saturations were 80 per cent and 88 per cent respectively Since the brachial artery saturation was lower than that of the femoral artery, it was thought that the diagnosis of aortic pulmonic window was more likely than that of patent ductus arteriosus with reversal of flow

At the time of operation a diagnosis of patent ductus arteriosus was confirmed A lung biopsy showed considerable medial hypertrophy and intimal proliferation in the small branches of the pulmonary artery These findings were especially prominent in the arteries measuring under 100 microns in diameter where the arterial lumen was found to be nearly obliterated in several instances This was thought to be grade III pulmonary arterial and arteriolar sclerosis A corrective operation was not attempted at the time of exploratory thoracotomy

The two cases described both presented the common complaint of progressively severe exertional dyspnea Case 1 presented the more typical physical finding of regional cyanosis and clubbing limited to the lower extremities [7] Variations of this sign have been reported since there may be retrograde flow of pulmonary artery blood into the left subclavian artery or even into the root of the aorta causing cyanosis of the upper portions of the body in general This latter and more atypical physical finding was present in Case 2 at the time of her exploratory operation The retrograde flow of desaturated pulmonary artery blood into the aortic root had been well demonstrated in one other instance [8] The first case showed the usual findings of polycythemia, right ventricular hypertrophy on fluoroscopy, and a right ventricular strain pattern electrocardiographically with large pulmonary artery segments In her case, a well calcified ductus arteriosus could also be seen and demonstrated on the x-ray films Case 2 had apparently not been in a state of reversal long enough to result in the development of polycythemia However, a regurgitant murmur of the Graham-Steell type was heard although the pulmonary systolic murmur was much the more prominent of the two

That pulmonary hypertension may be progressive and that reversal of flow may occur relatively late in life, supporting the idea that the hypertension may be acquired rather than congenital, is demonstrated by the clinical course of Case 2

It is generally agreed that the division of a ductus arteriosus when there is a significant (net) right to left shunt unless the patient is supported by some other procedure designed to maintain flow into the left ventricle is likely to prove fatal One case in which the two circulations seemed to be "in-balance"—virtually equal pressures in aorta and pulmonary artery with bidirectional shunt and not truly continuous reversal of flow—has been operated on with survival of the patient In this instance the ductus arteriosus was not completely divided and there have been no follow-up studies to determine if the communication has been completely closed [9] The theoretical possibility exists that merely to divide such a "balanced" shunt, particularly in an adult, might do little to cure the existing pulmonary hypertension

The effects on the pulmonary artery pressure of breathing 100 per cent oxygen have been well-studied and the chief result has been an inverse relationship between the oxygen tension of the inspired air and the pulmonary artery pressure.[8] In the presence of patent ductus arteriosus with reversal of blood flow the result should then be an *increase in the saturation* of femoral artery blood. It has been well-demonstrated that the opposite occurs when the O_2 content of the inspired air is reduced to a level of 10 to 14 per cent, the amount of the reduction in saturation ranging between 2.2 and 9.8 vol per cent.[8] Whether or not these alterations occur in a given case would seem to depend on the degree of sclerosis of the small pulmonary arteries and arterioles. In Case 1 the *femoral artery saturation* rose from 53 to 74 per cent in 1951 after breathing 100 per cent O_2 while a repeat similar study in 1954 showed a rise from only 60 to 69 per cent, suggesting the possibility that the pulmonary arteriosclerosis had progressed during the interval to the point that relatively little reduction in the pulmonary vascular resistance could accrue from the breathing of 100 per cent O_2. (Table II)

The basic reason why the adult with patent ductus arteriosus develops pulmonary hypertension and eventually reversal of flow is not entirely clear although the same problem exists in reference to other left to right shunts. Recent animal sudies may give a clue.

From the relationship

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

it is apparent that increases in pulmonary artery flow can result in increased pulmonary artery pressure provided the pulmonary vascular resistance remains constant or does not decrease excessively. That this does occur has been amply demonstrated by experience with the closure of atrial septal defects wherein distinct elevations of pressure in the pulmonary artery prior to operation are no longer present following closure of the defect and reduction of the pulmonary artery flow to normal. The highest pulmonary artery pressure we have observed to date with a simple atrial defect was 72/34 mm. Hg.—moderately severe pulmonary hypertension apparently based on increased flow alone but not enough to cause reversal of the shunt and cyanosis. Following closure of the defect, the right ventricular pressure was found to be 28/4 mm. Hg.—a normal value. There are scattered reports of moderate pulmonary hypertension in the presence of a patent ductus arteriosus reverting towards normal following surgery—from 100 mm. Hg. to 40 mm. Hg. in one case—apparently because the elevation in pressure originally depended almost entirely on *increased* pulmonary blood flow.[10] The same reduction occurs in certain instances following correction of ventricular septal defects.

A second aspect of the problem has to do with increased pulmonary vascular resistance resulting from increased pulmonary flow. In two series of experiments,[11,12] pulmonary hypertension has been consistently produced in dogs by the anastomosis of a systemic artery and a branch of the pulmonary artery. In each series marked changes in the pulmonary arteriolar structure occurred, including the appearance of medial muscular

hypertrophy and intimal fibrosis Serial lung biopsies demonstrated the development of arteriolar medial muscular hypertrophy within a two-week period following the anastomosis, followed in turn by intimal fibrosis and and increase in the adventitial collagenous material over a two to three-month interval No changes in alveoli, capillaries, or veins were noted [12] The striking similarity of the changes to those noticed in humans with increased pulmonary vascular resistance has already been emphasized [11] In some instances the smaller vessels are completely obliterated That the size of the lumen in the pulmonary arteriole is the more important factor in determining pulmonary vascular resistance than is the increased viscosity of blood relative to polycythemia or other similar factors has also been demonstrated [13]

It was further observed that the total amount of increase in pulmonary blood flow was not the sole factor in initiating the changes subsequently observed in pulmonary arteriolar structure and in pulmonary artery pressure The type of anastomosis formed—whether end-to-end or side-to-side—was contributory in some way, the end-to-end anastomosis resulting in the greater amount of change It has been suggested that the pulse wave form is of some significance and that the pulsatile thrust of blood into the pulmonary circuit is responsible in part for the changes observed [12] Whether or not this is an important factor in the human cannot as yet be determined The usual patent ductus arteriosus and aortic-pulmonic window function as side-to-side anastomoses in which the shunt is not obligatory In the adult, for the former, the development of severe degrees of pulmonary hypertension is uncommon A large ventricular septal defect approaching functionally a single ventricle probably more closely simulates the situation in the experimental animal and here marked pulmonary hypertension is necessary for survival, provided that pulmonary stenosis is not present Simple atrial septal defects seem not to be ordinarily accompanied by severe pulmonary hypertension whereas atrioventricularis communis defects seem commonly to have marked elevations in pulmonary artery pressure These are impressions not as yet statistically proved They would suggest, however, that the presence of a large, pulsatile thrust through an obligatory shunt may be related to the development of the severe forms of pulmonary hypertension The ordinary Blalock anastomosis does not duplicate this experimental situation There are rare instances in which end-to-end anastomoses have been made in the adult between a systemic artery and the right or left pulmonary artery but none of these have had post-operative studies that would shed any light on this particular problem

From the evidence at hand it would seem that a reasonable working hypothesis can be formulated to explain the course of events in the adult who develops pulmonary hypertension in the presence of a left-to right shunt It is known that increased pulmonary flow may in itself produce pulmonary hypertension and it is suggested that this in turn leads to anatomical changes within the small pulmonary arteries resulting in an increased pulmonary vascular resistance and with it a further aggravation

of the pulmonary hypertension The presence of a pulsatile thrust of blood into the pulmonary circuit may also be of great importance

One interesting question concerns whether or not these changes observed in the pulmonary arteriole in the severe types of pulmonary hypertension are reversible It is not known if such regression occurs in man The experimental preparation does show a regression of the anatomical changes in the pulmonary arteriole following correction of the systemic artery-pulmonary artery anastomosis These changes occur very slowly over a prolonged period of time and in no animal thus far have the pulmonary arterioles returned entirely to normal [14] The possibility of such regression occurring in man seems good enough to warrant further attempts at repairing surgically the patent ductus arteriosus in which reversal of flow has occurred

The mechanism of death in the first case described, and in some others, has been ventricular fibrillation It seems reasonable to assume that with obliteration of the ductus arteriosus and because of markedly increased pulmonary vascular resistance, the right ventricle is unable to maintain enough flow through the lungs and into the coronary circulation to perfuse adequately the myocardium Under such circumstances ventricular fibrillation may easily occur This constitutes a major problem that must be solved before the repair of this anomaly will become possible

SUMMARY

1 Two examples of patent ductus arteriosus with pulmonary hypertension, reversal of flow, and cyanosis occurring in adults are described

2 In Case 1 changes in the response to breathing 100 per cent O_2, as determined by studies of femoral oxygen saturations, suggest that the pulmonary vascular resistance became "fixed" as the disease progressed

3 Clinical and experimental observations demonstrated that increased pulmonary blood flow results in pulmonary hypertension that may in turn be followed by pulmonary arteriolar, medial, and intimal thickening and increasing pulmonary vascular resistance This is especially true if the flow is of the pulsatile type

4 The pulmonary arteriolar changes in the experimental animal are but partially reversed during reasonable intervals of observation once the pulmonary pressure has been restored to approximately normal values

5 For surgery to be successful in cases with marked reversal of flow some mechanism for maintaining adequate coronary flow and preventing ventricular fibrillation will be required

RESUMEN

1 Se describen dos casos de conducto arterioso presistente con hipertensión pulmonar, inversión de la corriente y cianosis en adultos

2 En el caso 1, los cambois en la respuesta a respirar 100 por ciento, como se pudo determinar por los estudios de la saturación de oxígeno

femoral, sugieren que la resistencia pulmonar vascular se volvió "fija" al progresar la enfermedad

3 Las observaciones clínicas y experimentales demostraron que el aumento del flujo sanguíneo pulmonar da por resultado la hiperstensión pulmonar que a su vez puede ser seguida por engrosamiento de la íntima arterional, así como engrosamiento de la media, y un aumento de la resistencia pulmonar Esto es especialmente cierto si el flujo es de tipo pulsátil

4 Los cambios pulmonares arteriolares en el animal de experimentación, sólo son parcialmente invertidos durante intervalos razonables de la observación una vez la presión pulmonar se ha restablecido aproximadamente a los valores normales

5 Para que la cirugía tenga buen resultado en casos con marcada inversión del flujo se requerirá algún mecanismo para mantener el flujo coronario adecuado y para prevenir la fibrilación ventricular

RESUME

1 Les auteurs décrivent leux exemples de persistance du trou de Botal avec hypertension pulmonaire, inversion du courant sanguin, et cyanose apparus chez des adultes

2 Les altérations du cas I apparaissant lors de l'épreuve de la respiration à 100%, déterminée par l'étude de la saturation oxygénée de l'artère fémorale, donnent à penser que la resistance des vaisseaux pulmonaires s'était "fixée" alors que l'affection continuait sa progression

3 Des observations cliniques et expérimentales ont démontré que l'augmentation de la circulation sanguine pulmonaire dépend de l'hypertension pulmonaire qui à son tour peut être suivie par un épaississement de la média et de l'intima des artérioles pulmonaires entraînant un accroissement de la résistance vasculaire pulmonaire Ceci est particulièrement vrai si le débit est du type pulsatile

4 Les altérations artériolaires pulmonaires chez les animaux d'expérience ne sont que partiellement réversibles pendant des intervalles raisonnables d'observation une fois que la pression pulmonaire est revenue à son taux approximativement normal

5 Pour mener à bien les interventions dans les cas avec trouble marqué du débit, on doit arriver à maintenir un débit coronaire convenable, et prévenir la fibrillation ventriculaire

ZUSAMMENFASSUNG

1 Es werden zwei Beispiele beschrieben von offenem ductus arteriosus mit pulmonalem Hochdruck, umgekehrter Stromungsrichtung und cyanose bei Ewachsenen

2 Der Wechsel von 100% in der Antwort von Fall I bei der Atmung, wie aus Untersuchungen bei der Prufung von femoralen Sauerstoffsattigungen hervorging, lasst vermuten, dass der pulmonale Gefasswiderstand zu einem "fixierten" wurde in dem Masse, wie sich die Krankheit weiter entwickelte

3 Durch klinische und experimentelle Beobachtungen wurde nachgewiesen, dass eine erhohte pulmonale Durchstromung eine pulmonale Hypertension zur Folge hat, die ihrerseits gefolgt sein kann von einer pulmonalen arteriolaren Media-Intema-Verdickung und erhohtem pulmonalem Gefasswiderstand Dies ist besonders dann der Fall, wenn die Durchstromung vom pulsierenden Typ ist

4 Die Veranderungen an den pulmonalen Arteriolen im Tierversuch lassen sich jedoch wenigstens teilweise wieder aufheben innerhalb ubersehbarer Beobachtungszeitraume, wenn der pulmonale Druck erst einmal wieder auf annahernd normale Werte eingestellt ist

5 Damit ein operativer Eingriff zum Erfolg fuhrt in Fallen mit ausgesprochener Umkehr der Durchstromung, sind eine Reihe von Vorkehrungen zur Aufvechterhaltung einer ausreichenden coronaren Durchstromung und Vermeidung von Kammerflimmern erforderlich

REFERENCES

1 Gross, R E "The Patent Ductus Arteriosus Observations on the Diagnosis and Therapy in 525 Surgically Treated Cases," *Am J Med*, 12 472, 1952

2 Holman, E "Certain Types of Congenital Heart Disease Interpreted as Intracardiac Arteriovenous and Venoarterial Fistulae 1 Patent Ductus Arteriosus," *Bull Johns Hopkins Hosp*, 36 61, 1925

3 Johnson, R E, Wermer, P, Kuschner, M and Cournand, A "Intermittent Reversal of Flow in a Case of Patent Ductus Arteriosus A Physiologic Study with Anatomic Findings," *Circulation*, 1 1293, 1950

4 Hultgren, H, Selzer, A, Purdy, A and Gerbode, F "The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension," *Circulation*, 8 15, 1953

5 Dammann, J F, Jr, Berthrong, M and Bing, R J "Reverse Ductus A Presentation of the Syndrome of Patency of the Ductus Arteriosus with Pulmonary Hypertension and a Shunting of Blood from Pulmonary Artery to Aorta," *Bull Johns Hopkins Hosp*, 92 128, 1953

6 Lukas, D S, Araujo, J and Steinberg, I "The Syndrome of Patent Ductus Arteriosus with Reversal of Flow," *Am J Med*, 17 298, 1954

7 Bothwell, T H, VanLingen, B, Whidborne, J, Kaye, J, McGregor, M and Elliott, G A "Patent Ductus Arteriosus with Partial Reversal of the Shunt," *Amer Heart J*, 44 360, 1952

8 Burchell, H B, Swan, H J C and Wood, E H "Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation of Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension," *Circulation*, 8 681, 1953

9 Kattus, A A and Muller, W H, Jr "Patent Ductus Arteriosus with Reversal of Blood Flow Report of a Successful Closure and Physiological Studies," *Ann Surg*, 138 870, 1953

10 Adams, F H "Pulmonary Hypertension in Children Due to Congenital Heart Disease," *J Pediatrics*, 40 42, 1952

11 Muller, W H, Jr, Dammann, J F, Jr and Head, W H, Jr "Changes in the Pulmonary Vessels Produced by Experimental Pulmonary Hypertension," *Surgery*, 34 363, 1953

12 Ferguson, D J and Varco, R L "The Relation of Blood Pressure and Flow to the Development and Regression of Experimentally Induced Pulmonary Arteriosclerosis," *Circulation Research*, 8 152, 1955

13 Dexter, L, Dow, J W, Haynes, F W, Whittenberger, J L, Ferris, B G, Goodale, W T and Hellems, H K "Studies of the Pulmonary Circulation in Man at Rest Normal Variations and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressures and High Pulmonary 'Capillary' Pressures," *J Clin Investigation*, 26 561, 1950

14 Ferguson, D J, Berkas, E M and Varco, R L "Process of Healing in Experimental Pulmonary Arteriosclerosis," *Proc Soc Exp Biol Med*, 89 492, 1955

Noises Heard at a Distance from the Chest

Second Series*

WILLIAM BENNETT BEAN, M D , F C C P **
Iowa City, Iowa

"The abnormal murmurs, as well as the natural sounds of the heart are heard to a greater distance in proportion to their mere loudness, and that not only in the direction to which the current of the blood conducts them, but in all directions" —*Latham*

We are gathered on this occasion of physical and mental refreshment to do honor to the memory of Louis Mark who is no longer among us In this materialistic age, we are self-conscious about anything which smacks of hero worship Too often we forget our illustrious forebears and our cherished friends Of all the professions, medicine leans most heavily on the past and loses most when it fails to remember its heritage I hope my words tonight would have pleased Louis Mark, whose personality and contributions to chest disease did not prevent an enjoyment of fun in matters most austere and serious

Once every second at least, four thousand times or more an hour, a hundred thousand times a day, sleeping and waking, active and quiet, heedful and heedless, our heart beats out its irrevocable time Our pulse, a living pendulum of life, tells for us all the seconds, minutes, and hours that will never return Who has not wondered at the long procession of these heartbeats on the ineluctible abscissa of time This silent measure of the tides of life seem tireless as well as timeless But upon occasions its quiet may be interrupted by strange sounds, sounds so loud that they escape the little sonic barrier of the chest The beats become ominously loud The uproar may grow insistent Sometimes it gets amazed attention from the person who is making the loud noises and anyone else within hearing range I wish to deal this evening with such noises as they have occurred in my own experience and in reports which I have gathered from a variety of physicians and medical writings This topic is one of my avocations in medicine It illustrates the ancient dictum that rare things teach us truth about commonplace things, and that what begins off the the beaten path may become a royal road of interest

Some 15 years ago I began the curious hobby of collecting references to precordial noises heard by the unaided ear at a distance from the chest I was on the lookout for examples I found them Indeed, my first interest was aroused by hearing such a noise Four years ago, I used this collection as the basis of the Roger Morris lecture in Cincinnati Later

*The Second Annual Louis Mark Memorial Address, presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

**From the Department of Medicine of the College of Medicine and the University Hospitals, State University of Iowa

it was published.[1] I was hardly prepared for the deluge of letters, phone calls, and reprints which descended upon me. Apparently I had poached on the hobby of many physicians. Some chided me for failing to mention their paper. One was annoyed somehow that I had not included his favorite case, though he had neglected to publish it. Getting into that important medical journal, *Time*, produced the usual response of people with ticking ears, barking chests and such like, including a frantic Sunday call from a banker in South America whose ear ticked like a watch, though I could not identify it over the phone. Apparently it confused him when he tried to count his money.

I omit the embarrassing borborygmi of the dowager, famed in story and limerick, the infinitely varied sounds of wind from belches or escaping flatus, the 'tic'-tick of audible clicks in the ear, nose and throat which others as well as the unhappy victim may hear when intratympanic, palatine or eustachean tube muscles twitch after the manner of muscles about the eye when one is tired, and I omit also even the fleeting cry of the unborn babe in utero protesting rude expulsion into the outer world, the *vagitatus uterinus* which haunts the hearers. Omitting these and other unlikely sounds, the patient or physician may be startled by noises emanating from the chest produced by action of the heart and heard at a distance by the unaided ear.

Ancient medical records have no references to such sounds. The Bible has no precordial companion for the abdominal rumblings of Isaiah "whose bowels sound like an harp." There is no thoracic counterpart of the borborygmal chorus of Aristophanes' "Clouds." Only with the perfection of the art and science of physical diagnosis was an interest in normal pulmonary and cardiac sounds and noises developed sufficiently to recognize abnormal sounds.

Chest and Mediastinum

Dr. Richard Asher of London sent me the story told by his former chief, the late Dr. Theodore Thompson who had a patient with a large chronic hydropneumothorax.[2] He was a sturdy fellow and a keen huntsman. He continued to follow the hounds, for he never let his trouble become a disability. On occasions when his horse jumped a hedge and brook, members of the hunt in close pursuit thought that he had landed in the water because of the great roaring splash. To their astonishment, he would go galloping on unharmed, leaving the hunt in consternation. The noise was merely the splashing of his hydropneumothorax.

Traumatic pneumothorax must surely have produced loud noises in ancient wars and accidents. Medical reports go back a mere hundred years when Bricheteau[3] described such noises after crushing injury to the chest. The *bruit de moulin* — the noise of a mill wheel, happily combines the rhythmic splashing and the background throb of the wooden machinery. Captain Rees and Hughes[4] in the British Army in World War I rediscovered the sign and called it pericardial knock. Their report prompted Henley Munden[5] to record a mischance of sport and the risks

of rabbiting in this note "I was called to see a boy who had been accidentally shot in the head and left side of the chest when rabbiting About an hour before he died a loud cardiac 'click' developed which was synchronous with the heart systole and could be heard distinctly six or eight feet away It bore no relation to the respiratory movements, as the respiration was Cheyne-Stokes in character and the sound persisted during the period of aponea The click in the ear-piece of a telephone when the lever is raised illustrates it very well During the last fifteen minutes of life the heart became very feeble and irregular and the 'click' disappeared"

Spontaneous and Induced Pneumothorax

Pneumothorax is a common cause of loud noises Readers of Thomas Mann's *Magic Mountain* will recall his vivid description of the noises of pneumothorax Fourteen new records, mostly from personal letters, indicate its frequency Scadding and Wood[6] reported a case which probably holds the indoor record for loudness They told of a young man in perfect health who had a 'sharp pain in the chest, and this was followed by an extremely loud peculiar noise accompanying the heart beat The noise was so loud that it could be heard in the room below' Three weeks later it disappeared without complication, despite the diagnosis of rupture of a heart valve

Interstitial Emphysema of Lung and Mediastinum

I had the great good fortune to observe one of Louis Hamman's[8] early patients with interstitial emphysema, though there were no distantly heard sounds One patient he described as follows "A 51-year-old physician had pain in the chest while shaving On the following evening of the next day while 'lying upon his left side, he heard a curious loud, bubbling sound with each contraction of the heart His wife sitting upon the bed beside him could hear it very plainly'"

A number of case reports mention loud murmurs as well as the more usual sounds heard only with the stethoscope Pinckney[8] reported

A 24 year old white woman who had six different attacks of spontaneous pneumothorax, in some of which there was interstitial emphysema On her third attack she had dull pain and dyspnea "She also noted a loud, clicking, snapping noise audible at all times no matter what position she assumed In addition when lying on the left side she heard another sound, a crunching, crackling sound like small chicken bones being crushed This sound she cannot say with certainty was synchronous with her heart beat Both sounds were easily audible to persons in the room with her" On her fourth attack three months later, pain developed while she was walking Several hours afterward there was a loud clicking noise, and a crunching sound became audible Roentgenograms showed a small pneumothorax on the left side With her fifth attack 15 months later, she had only a heavy sensation "Again the very loud clicking noise, synchronous with each heart beat, was easily audible to anyone within twenty or more feet, and slightly less audible was the crunching noise when she sat leaning forward on her left side" This lasted for six weeks, during which time her lung reexpanded

Alimentary Canal

Recently I found Curtin's[9] report of cardio-esophageal gush and click He reported three cases In one, the story is as follows

In 1894, a girl, nineteen years old, called at my office, saying that she had a queer noise which a doctor had told her was a heart murmur that he could hear without applying the ear to the chest She informed me that it was not so loud that day, for she could not hear it I listened to her chest and found a mild, double, mitral murmur, with evidence of some hypertrophy She then complained of dyspeptic symptoms only I told her to return to me if the sound came back, which she did next day I could then hear a sound with the action of the heart, *which was then excited, and, on* withdrawing my ear one yard from the chest, I could hear a sound, which was before or early in the systole, when her mouth was open When she closed her mouth the sound was very perceptibly deadened It continued when her breath was held On applying the ear to the chest the sound was subdued, being less distinct than when the ear was held in front of the open mouth It sounded like a short gush of air from the throat modified by the upper air passages, giving it a low-pitched, grunting sound I could get no sound at the epigastrium and there was no apparent effort of the diaphragm or abdominal walls as if expelling flatus from the stomach The sound continued while she was talking and breathing It did not appear to be a moan or grunt like a regurgitation of air from the stomach

I gave her some potassium bromide, tincture of nux vomica, and compound tincture of cardamon and mint water She called next day and I found that the heart had quieted down and the sound promptly disappeared

Dr Lewis January[10] called to my attention a rare instance of a healthy *young man whose heart sounds were clearly audible several inches from* his mouth when it was held open He had no heart disease X-ray study of the chest, esophagus, and upper gastrointestinal tract showed them to be normal Perhaps some anatomic quirk permitted his esophagus to be patulous when his mouth was open and to act as a megaphone

I offer an autobiographical note Occasionally, when my stomach contains just the proper quantity of fluid and air, a happy postprandial mixture, and when semirecumbent in an easy chair, a systolic tinkle or splash is clearly audible to me and very diverting It has been heard by others a foot away The cardiac impulse on the diaphragm and stomach obviously produces the sound. It generally vanishes after a few minutes or can be eliminated by belching, but swallowing air or air and water has not brought it back at will

Greene,[11] Allan[12] and others have reported similar cases Occasionally in Machella's splenic flexure syndrome gas in a high riding colon may provide a drum on which the heart may beat away merrily through the diaphragm Several hundred years ago Nicolas Tulp[13] had this strange tale of a reverberating spleen to tell

Nothing in medical art is better known than that the spleen pulsates continually, if violently moved by the arteries But for this organ itself to strike the ribs so forcibly that the sound of the beating (lit flogging, or whipping) may be heard from afar, that certainly is novel, and perchance hitherto unheard of

In the case of Nicolaus Fabius, an active man, but rather frequently afflicted with black bile, a hardened (indurated) spleen made so forceful an impulse on the adjacent ribs, that not only he himself felt pain therefrom, but persons at a considerable distance might clearly hear the sound of the beats, and even so distinctly that one might count the separate impulses, and with the close-pressed hand feel the throb of the beating spleen

In fact, I remember that in company with Henricus Saulius, the physician of Utrecht, I heard these repeated sounds at a distance of above thirty paces

Pneumoperitoneum In my original paper, I had not found any example of pneumoperitoneum associated with sounds heard at a distance Since that time, I have the record of the following patient whose noises caused her much amusement Dr Fisher[14] of Providence, Rhode Island, related to me the following facts

The patient was a 26 year old housewife seen first on the 30th of October, 1949, highly amused because of a clicking noise which occurred in her chest when she sat up When she awoke at 2 a m to feed her infant son, she was suddenly aware of some pain between the shoulders and heard the clicking sound Lying at an angle of 45° or less, the sound became inaudible No abnormality could be found except that her heart made a sound like striking a ping-pong ball with a racket or clicking a telephone receiver, whenever she sat upright After the first symptom, there were no further sensations On fluoroscopic examination, air was noted beneath both sides of the diaphragm There was no pleural or pericardial effusion After three or four days, the noise disappeared completely She remained subjectively well through the whole episode The air got into her peritoneum in this wise Her third child had been born three weeks previously After a few days in the hospital and a few more days of rest at home she was up and about Her obstetrician had suggested that she perform knee-chest exercises two or three times a day She was not only athletic and very sturdily built, but had a proper New England conscience, so that she faithfully performed these exercises with great vigor With the violence of her exercise and a patent cervix, she had achieved a do-it-yourself Rubin's test and introduced air into the peritoneum I need not stress the lesson this bears for women in the postpartum period or knee chest position

Heart

Edgar Allen Poe told an eerie tale of a murderer who buried the victim's corpse under the floor but was undone because his victim's heart beat with such insistent loudness that it drove the unhappy slayer to madness and final confession Readers of James Barrie will recognize in Peter Pan the unpremeditated preview of the noises of the Hufnagel valve in the crocodile which swallowed an alarm clock and walked about ticking merrily and mysteriously from his unusual meal Audible manifestations of the heart's activity, are an interesting though motley tribe Perhaps it is fortunate that they are rare lest a systolic knock or an off-beat ping in our machinery be seized upon by fabricators of modern advertising mythology as resulting from a low vitamin octane rating

Pneumoperitoneum Even before Laennec's observation, Morgagni spoke of having heard the splash of water and air in the pericardium Portal encountered this combination at autopsy without recording the clinical findings Brichteau in 1844 described a Polish veteran of Napoleon's army who was struck down by a blow on the chest with a carriage tongue His wife heard "boiling" in his chest, and Brichteau and eight assistants heard it The man died Autopsy disclosed pericarditis, with much evil-smelling gas Stokes observed a lad whose trouble began with dry pericarditis but "later the sounds became so loud and singular that the patient and his wife, who occupied the same apartment, were unable to obtain a moment's repose On examination, a series of sounds was observable which I had never before met with It is difficult or impossible to convey in words any idea of the extraordinary phenomena then presented They were not the rasping sounds of indurated lymph, or the leather creak of Collin, nor those proceeding from pericarditis with valvular murmur, but a mixture of the various attrition murmurs with a large crepitating and gurgling sound, while to all of these phenomena was added a distinct metallic character, and I could form no conclusion but that the pericardium contained air in addition to an effusion of serum and coaguable lymph"

James[15] surveyed the whole problem of pneumopericardium adding a case of his own Perhaps the most remarkable example was Walshe's[16]

poor sword swallower who, during a lapse of attention, had the melancholy experience of piercing his gullet with the sword Air was let into the pericardium and the unadvertised sound effects were heard with amazement by the audience

Air embolism Anyone who has heard the awful sound of air sucked in through open neck veins, churning in the heart, or seen the patient die promptly realizes why few cases are reported Fortunately the accident is fairly rare

Heart murmurs Lack of interest in natural phenomena probably accounts for the fact that heart noises heard at a distance were first recorded about 150 years ago by Allan Burns [17] Laennec observed many women with nervous palpitation whose heart throbs he heard two inches to four feet away He postulated air in the cavities of the heart which Andral wisely discredited Curiously Laennec, on his own death bed, had precordial noises audible several feet away In one of Stoke's patients,[18] loud noises were "the principle cause of his suffering for his general health long continued excellent, and the heart's action was but little excited This gentleman once observed to me that his entire body was one humming-top The loudness of the tone varied with the force of the heart When I first saw him the sounds were audible at a distance of at least three feet, but when the force of the heart had been reduced the loudness of the sound at the aortic orifice was so much reduced as to render it inaudible, unless by applying the ear " Humming was heard over the limbs, probably transmitted by bone

Some 30 years ago, or thereabouts, O H Perry Pepper used to relate the following story to his students [19] He said that in his early days he was called in consultation to see a teen-age boy He lived in a small street The house was a typical Philadelphia two-story row house with four or five white marble steps leading up to the doorway It was a warm day and the windows were open As he stood on the doorstep waiting for the bell to be answered, he heard a rhythmical slapping or thumping sound which obviously came from the second story front bedroom When he got upstairs to see the patient, he found a thin boy with active rheumatic heart disease, an enlarged heart, and a distended stomach containing air and fluid The sound which he had heard on the doorstep was produced by the overactive heart percussing the stomach through the diaphragm Dr Pepper was kind enough to send me a reprint of his essay on "Magnified Heart sounds Due to Extracardiac Conditions with Report of an Unusual Case" published in 1912 in which a slightly reduced description of the patient is given in extensive detail [20] It loses none of its charm from sticking more closely to facts

Rupture of the aortic valve produces a murmur which may be heard at a distance In his classic study, C P Howard,[21] one of my predecessors in the Chair of Medicine at Iowa, described 21 cases in which the murmur was heard by the patient and his friends This number represented about a third of the nontraumatic cases The variations in loudness of the sound are illustrated by the following reports Quain's case, heard several

inches from the chest, O'Neill, 6 ft , Dupuis, 15 to 20 cm , Tranquilli, 50 cm , Schneider, 25 cm , and Schlecht, several centimeters The murmur has been compared to the "croaking of a frog," "cooing of a dove or pigeon," as a "rumbling, rustling noise," a "humming noise," a "whistling noise," a "buzzing in the chest," a "musical murmur or trill," a "whining noise," and even a "rattle in the head "

Dr Hubert Royster,[22] a distinguished surgeon of North Carolina, sent me the following story after he had read my tale of Precordial Noises Long ago he saw in his office a negro lad, rather rheumatic in appearance He had a heart murmur of the cooing dove type so loud that it could be heard across the small office He had a pigeon breast deformity too From the description of his murmur and the deformity, his family came under the happy misapprehension that he had "a pigeon in his breast " He lived for many years and died finally of congestive failure, keeping the murmur until the end

Bellet and his associates (23) have made a notable contribution to the problem of precordial noises in their articles on musical murmurs of aortic insufficiency They emphasized the part played by eversion of an aortic cusp diseased by syphilis In their first paper, only one of 11 patients had murmurs heard at a distance "The patient's bedfellow was considerably annoyed by the unusual and constant noise " In this and three other instances the murmurs were audible to the patient, presumably in the same distressing way as to Stokes' poor patient, who likened himself to a humming top This distinction between murmurs heard by a patient but not by others suggests that vibrations may be transmitted directly to the choclear apparatus through the bone, blood vessels, or other tissues of the body rather than by air transmission In their second series, four of 18 patients complained of hearing noises that interfered with sleep and made them nervous One man produced such a noise that it disturbed his wife at a distance of seven feet

While I was writing this section, an ancient squire from the Iowa farmland was brought in by a cluster of apprehensive descendants The old man's heart squeaked whenever he took a deep breath Nothing could be heard when I examined him unclothed "No, no," he said, "Only when I'm dressed " Sure enough, there was a staccato cardio-respiratory squeak during deep inspiration A little oil on his suspender pulley produced a dramatic cure The bewildered but grateful family marched away in triumph

Noises in the Head

When a patient complains of noises in the head, we immediately suppose that he is hearing voices but when we ourselves hear his noise we smile less wisely In an editorial review of intracranial bruits in the *Lancet* (24) there was no mention of such noises heard at a distance from the head However, Dr Taylor (25) wrote me of one such patient whose noise he could hear without a stethoscope Purves (26) and Wilcox (27) have each recorded similar findings The explanation for these noises is that they

arise from aneurysms, arteriovenous aneurysms, or unusual distortions of intracranial vessels

Obscure noises Some sounds heard at a distance from the chest defy precise classification An example of such strange cases is a footnote in Laennec's book on auscultation[25] Andral recorded a case as follows "I lately saw a woman who complained of palpitations of the heart Each stroke of this organ was accompanied by a peculiar gurgling sound, which evidently came from the precordial region, andw as heard only when the heart struck the ribs, it was perceptible at a distance" Frost and Bing[29] described a healthy 22 year old woman who was seized suddenly by a "crick in the back," a sensation that something had come loose in her chest, and then pain in the chest and left shoulder A blowing systolic murmur and some vague scratching sounds were heard along the left sternal border Sounds came from her precordium so loud that they were heard 3 m away. They were the synchronous with the heart beat and loudest when she was lying on her left side, disappearing when she turned to the right Phonocardiograms showed the sounds to be systolic in time but spaced at variable intervals from beat to beat Intensive studies failed to reveal any lesion of the lung, pleura, pericardium, or heart

Warburg[30] described a man with mitral stenosis and auricular fibrillation observed many times in congestive heart failure With an obscure infection he had fever and "he had heard a sound from his chest which

TABLE I
CONDITIONS CAUSING PRECORDIAL NOISES

		Total Series I and II 251 Cases	Per Cent Series II	Per Cent Series I 164 Cases
Heart murmurs		80	32	35
Pneumothorax		46	18	21
Spontaneous	30			
Traumatic	16			
Interstitial emphysema		36	14	16
Spontaneous	30			
Traumatic	6			
Pneumopericardium		27	11	15
Miscellaneous		16	6	4
Alimentary canal		13	5	5
Hufnagel valves		12	5	0
Air embolism		8	3	4
Unexplained		7	3	0
Aneurysm		4	2	0
Chest deformity		2	1	0

he described as though something were dripping, he said that he thought his heart had burst His wife was able to hear the sound when she was lying in the bed beside him I was able to verify his statements At every heart beat a clicking or slightly sonorous sound was audible in the room"

Levine and Harvey[31] recorded the case of a 45-year old woman with well-compensated mitral stenosis and auricular fibrillation After exercise, a weird sounding, rough musical murmur "was actually heard with the naked ear a foot away from the chest For several years she had been aware of a peculiar noise in her chest at times We have heard it at irregular intervals, sometimes only for a few seconds, at other times constantly and then it might be absent for days It is not related to position of the body or to breathing There is no x-ray evidence of diaphragmatic hernia or any other abnormality that might throw light on its causation"

A Digression into Veterinary Medicine

Shortly after my original paper appeared, Dr Eidsmoe[32] of Wisconsin told me of hearing his pony's heart thumping at a distance of 25 feet It sounded like a drum No explanation was available at the time but I find out from Dr Tjalma,[33] in our Institute of Agricultural Medicine, that there are several conditions in animals which may cause sounds which can be heard at a distance from the chest The common one is called bovine traumatic pericarditis The unique anatomy of the digestive system in cows predisposes the reticulum, the anterior and smallest of the four divisions of the ruminant stomach, to perforation caused by swallowing foreign bodies The reticulum lies against the diaphragm and the liver next to the diaphragm, and on the thoracic side lies the pericardial sac The normal eating habits of cattle, abetted by rural mechanization with wire bound hay bales, nails and screws lying about, may result in short pieces of metal being swallowed Because of the anatomical arrangements, foreign objects lodge in the reticulum Perforation of the reticulum by such objects is favored by its honeycombed mucous surface and the powerful force of its normal contractions Thus depending upon the size and shape of the object as well as the point of penetration, the reticulum, diaphragm and pericardium may be perforated in that sequence The ensuing pathological processes are obvious The resulting pneumopericarditis may be characterized by grossly audible splashing sounds An animal in this miserable condition usually assumes a peculiar stance with the "elbows" abducted as far as possible in an effort to reduce the pain and pressure As with the clinical counterparts, pneumopericardium, interstitial emphysema and pneumothorax in man, the sounds may not be audible at a distance but are heard readily with the stethoscope

Comment

Beyond serving as a repository for esoterica, is there usefulness in collecting such diverse disorders with the common denominator of noise

heard at a distance from the chest? Certain gleanings reward closer study. Loud heart murmurs are the commonest cause of the phenomenon, followed by interstitial emphysema, pneumothorax, and pneumopericardium. Records of the other conditions are less numerous. From the topographical and mechanical view, air free in the chest from the interstitial emphysema or pneumothorax, spontaneous or accidental, heads the list, cardiac murmurs come next and then pneumopericardium. Since the sources of this review have been casual and the survey sporadic, the data are not representative. In some specialties, particular problems may be missing or too heavily represented. A surgeon's reading and experience would no doubt assemble a different array.

The general problem may be considered in interstitial emphysema of the lung. In such a disturbance noises heard at a distance are an exaggeration of a sign much oftener confined to the chest and heard only with the stethoscope. Noises heard at a distance may be so loud as to command instant notice or may be heard by the unaided ear only after being heard with the stethoscope and then listened for attentively. Phonocardiographic records, of which several are reported, serve to demonstrate the sometimes irregular timing of such noises during systole and perhaps quiet the suspicion of skeptics that they are illusions. What constitutes the urge to publish case reports has never been known, but one has only to hear these eerie sounds to appreciate the high clinical drama. Published cases represent an unknown fraction of those met clinically. Illuminating papers, such as Louis Hamman produced, were followed by a wave of case reports, and a useful diagnostic sign caught popular fancy and became a medical fashion.

Clinical features of spontaneous interstitial emphysema of the lung may suggest acute myocardial infarction, but usually the complaint of pain in the chest is more insistent than the meager signs of difficulty. The patient is in pain but looks well, usually breathes easily, and is not in shock. Generally he is young, vigorous, and active, without signs or a history of hypertension, angina, or vascular disease. Later reactions, such as fever, leukocytosis, and rapid erythrocyte sedimentation, do not follow. Such a loud noise may be produced only in certain positions, so that change of position or movement will enhance or quiet the ticking chest. The noises have been audible at a distance in about 10 per cent of the recorded cases. The loudest noise, measured in distance heard, was perceived 20 feet from the patient. Duration varied from two hours to two weeks. There was much variation in the intensity, sometimes everything would be quiet and then the sounds would return. As a general rule, they would come and go. In all except one case, the sounds were heard best with the patient lying on the left side, and many could demonstrate the sound at will by assuming the proper position. I saw one young man whose main distress was not the pain in the chest but the fact that the noise coming from his chest was so loud his wife made him sleep in the next room. He could not turn and eliminate it, but finally it went away, and he gained his reprieve. Several other reports

suggest that such noises are a rare cause of temporary domestic infelicity They alarm patient and family Indeed, fear and curiosity occasionally have brought the patient to the doctor, since there may be little pain

Subcutaneous emphysema has been recorded in only a few cases, but since it may be confined to a small area and be ephemeral it is easily overlooked In almost all cases of interstitial emphysema of the lung, if complicating pneumothorax occurred it was on the left side Often it has been so small that only careful search with proper alignment has produced diagnostic roentgenographic shadows Right-sided pneumothorax does not appear to be rarer than left-sided, but only rarely has it been found in association with the crunching, bubbling, paper-rustling sound (Hamman's sign) so characteristic of mediastinal emphysema The most comprehensive discussion of such sounds in interstitial emphysema was given by Greene, who differentiated between two classes of sounds "The bubbling, crunching, clicking and some of the tapping sounds are due to the heart rubbing against emphysematous blebs in interstitial emphysema of the lung and mediastinum The knocking and tapping metallic sounds, on the other hand, are due to the heart striking an emphysematous bleb on the median aspect of a partly collapsed left lung or the diaphragm immediately over a gas bubble in the splenic flexure of the colon in the presence of pneumothorax on the left side" The evidence on which these conclusions are based is the fruit of careful study, and, short of detailed human experiments, is the best we are likely to get from observing the effects of accidents and disease

Diagnosis of such rare conditions is important, since the cause may be a mechanical crisis that can be corrected or eased Delay or confusion may be fatal On the other hand, if the casual condition is innocuous, it is well to avoid mistaking it for conditions of ominous import In order of urgency, the Muhlengeräusch or mill wheel sound of air embolism stands first Its clinical debut, always unexpected, is associated with an opening by wound, scalpel, or needle by which air gets into veins Immediate rotation to the left lateral position or the Trendelenburg position, trapping air bubbles above the blood in the right ventricle where they may be aspirated with a needle and syringe, may be lifesaving Inhalation of 100 per cent oxygen may help

Rupture of the esophagus, which I have seen produce Hamman's sign, probably can cause loud noises, even without pneumopericardium Since surgical cure in such a calamity may now be anticipated, the diagnosis of a ruptured gullet should be considered, especially in cases in which a history of extreme vomiting or instrumentation makes the condition probable

Traumatic pneumothorax, pneumopericardium, and pneumomediastinum with the connotation of crushed ribs or penetration by a missile or foreign body, obviously require urgent treatment The attending noise may indicate the extent of damage, which otherwise is not apparent Treatment is that of the underlying condition

Spontaneous interstitial emphysema of the lung implies pneumothorax

and, at times, the hazard of tuberculosis The noise heard at a distance has not been nearly so ominous as it has seemed to the victim, always amazed and often terrified by such uncanny behavior Thus, diagnosis usually permits reassurance, since in all recorded cases the patients have survived It should be kept in mind that tension pneumothorax may lurk under this clinical camouflage Also, "air lock," the dissection of air through the lung or hilum under pressure to impede blood flow, may require administration of 100 per cent oxygen or surgical intervention to stop the leak In general, the major role of the physician is to calm terror by bringing assurance

Noise from the alimentary canal may rarely lead to the discovery of hiatus hernia with an errant stomach or colon Loud murmurs, when they have arisen out of the innocuous quiet of the past, especially under some stress or accident, may call to mind the likelihood of ruptured aortic valve or the turning inside out of a syphilitic valve cusp Giving a better view of prognosis, such diagnostic tours de force escape the odium of academic banality

SUMMARY

A variety of clinical conditions that may be associated with precordial sounds heard by the unaided ear at a distance from the chest is assembled, compared, and assessed The commonest causes of such sounds are cardiac murmurs produced by valve rupture or other lesions, often abrupt in onset and a consequence of stress or strain Next in order of frequency come interstitial mediastinal and pulmonary emphysema, both spontaneous and traumatic These are followed by spontaneous and traumatic pneumothorax, pneumopericardium, noises the heart produces by striking air-containing gut, an embolus, and a small mysterious miscellany of unexplained sounds Since the noises have diverse sources there is no pathophysiological common denominator to compare with the clinical fact of abnormally great volume of sound With such differences in cause and, hence, in necessary treatment and prognosis, attention should be directed to the cause, which usually comes to light on careful clinical scrutiny

Four additional years of searching have added some new pearls to my strand, but it is far from complete I introduced the heresy that children do not have such sounds because they had small hearts and small thoracic sounding boards Looking for such noises, Dr John Wild and I found them nine times in children, even infants, with such lesions as ventricular septal defects, aortic or pulmonic stenosis or tricuspid atresia Hufnagel valves, being more prevalent, have added to the list Aortic aneurysms, going all the way back to Lancisi, have added four, and chest deformity, myxoma of the left auricle, ruptured tendinous cords, pneumoperitoneum and a murmuring spleen have swelled the list Our knowledge of the mysterious complexities of clinical medicine grows with experience perceived, understanding disciplined and inquiry directed We find what is there only if we sacrifice that part of ourselves which is given in complete attention and concentration *We see and hear what is*

there only if we look, listen, and focus We find what we search for not what we look at

If the spirit of Robert Hooke were with us tonight, his interest in natural phenomena would have had some stimulus, and perhaps he would be amused at my answers to his query, "Who knows but that one may discover the works performed in the several offices and shops of a man's body by the sounds they make, and thereby discover what instrument or engine is out of order!" This commemorative tribute I trust Louis Mark would have enjoyed and given his approval Finally, lest too much astringent mirth make you think the subject is not important, I conclude, in all humility, with a verse of scripture (Jeremiah 17 9) "The heart is deceitful above all things Who can know it "

Acknowledgments Collecting the material for this paper has been a very happy experience because though some of the noises described are tragic, many are not, and amusing and embarrassing situations may occur I have been particularly grateful to a large number of friends and strangers who have told me or written me about some specially fabulous case of their own or their personal experience with pneumothorax and interstitial emphysema Many, but not all, have been mentioned in the references I am grateful to Miss Nina A Frohwein for assistance with references I am particularly grateful to my secretaries, Mrs Charlotte Fell and Miss Eula Van Meter, for their patience with me and the numerous drafts of the paper, corrections, proofreading, for without them I would be lost

RESUMEN

Hay una variedad de afecciones que pueden asociarse a ruidos precordiales que se pueden escuchar con el oído a cierta distancia del pecho Estas afecciones se reumen, se comparan y se valúan Las causas más comunes son los soplos cardiacos producidos por ruptura valvular o por otra lesión a menudo de principio repentino y como consecuencia de esfuerzo o de "stress" Enseguida vienen por su frecuencia el enfisema mediastinal intersticial y enfisema pulmonar tanto espontáneos como traumáticos

Estos son seguidos por neumotorax espontaneo o traomatico, neumopericardio, o los ruidos que el corazón produce al golpear intestino conteniendo aire, embolias gaseosas y pequeños ruidos misteriosos no explicables Puesto que los ruidos tienen origines diversos no hay un denominador común fisiopatológico para comparar con el hecho clínico de los sonidos anormales de gran volumen Con tales diferencias causales debe procurarse investigar ésta para realizar el tratamiento necesario La causa puede aparecer generalmente después de cuidadosa investigación

Por cuatro años más de investigación he agregado nuevas perlas a mi colección, pero está muy lejos de ser completa Introduje la herejía de que los niños no tienen tales ruidos porque tienen corazones pequeños y pequeñas cajas de resonancia torácica Buscando tales ruidos el Dr John Wild y yo encontramos nueve en niños aún en infantes con tales lesiones como defectos septales ventriculares, estenosis aórtica y pulmonar o atresia tricuspídea Las válvulas de Hufnagel siendo ahora más comunes, se han agregado a la lista Los aneurismas aórticos retrocediendo hasta Lancisi han agregado cuatro, y la deformación torácica, el mixoma de la

aurícula izquierda, ruptura de las cuerdas tendinosas, neumoperitoneo y el soplo esplénico han hinchado la lista Nuestro conocimiento de las misteriosas complejidades de la medicina clínica, crece con la experiencia, con la disciplina e investigación dirigida Encontramos que así sucede si hacemos el sacrificio de nosotros concentrándonos en la tención Vemos y oimos si buscamos, escuchamos y enfocamos Encontramos lo que se busca no sólo lo que miramos Si el espíritu de Roberto Hooke estuviera con nosotros esta noche su interés en los fenómenos naturales sería de estímulo y probablemente le divertirían mis contestaciones a su pregunta "Quién sabe lo que uno podría descubrir?"

ZUSAMMENFASSUNG

Eine Vielzahl von klinischen Bedingungen wird zusammengestellt, verglichen und beurteilt, die verbunden sein konnen mit praecardialen Geräuschen, wie sie für das unbewaffnete Ohr entfernt von der Brustwand hörbar sind Die haufigste Ursache für solche Tone sind Herzgerausche, die durch Klappenruptur entstehen oder durch andere Veranderungen, oft abrupt im Beginn und als Folge einer Belastung oder einer Überanstrengung Am nachsten in der Reihenfolge der Haufigkeit kommt das interstitielle mediastinale und pulmonale Emphysem, sowohl das spontane wie das traumatische Darauf folgt im Rang der spontane und traumatische Pneumothorax, das Pneumopericard, Herzgeräusche entstanden durch anschlagenden lufthaltigen Darm, weiter folgt die Luftembolie und ein kleines ratselvolles Gemisch von nicht erklarbaren Gerauschen Weil die Tone verschiedene Quellen haben, gibt es keinen gemeinsamen pathophysio-logischen Nenner zum Vergleich des klinischen Tatbestandes eines abnorm grossen Geräusch-Volumens Mit solchen Unterschieden in der Entstehung und deshalb auch der notwendigen Behandlung und Prognose muss sich die Aufmerksamkeit auf die Ursache richten, die gewohnlich ans Licht kommt bei sorgfaltiger klinischer Überprüfung

4 weitere Jahre der Forschung haben mich zwar einige neue Erkenntnisse gewinnen lassen, aber es fehlt noch viel, um vollstandig zu werden Ich brachte die Irrlehre auf, wonach Kinder keine solchen Gerausche aufweisen, weil sie kleine Herzen haben und kleine thoracale Resonanzboden Auf der Suche nach solchen Gerauschen fanden Dr John Wild und ich sie 9-mal bei Kindern, sogar Kleinkindern, mit Befunden wie Ventrikel-Septum-Defekt, Aorten- und Pulmonal-Stenose oder Trikuspidal-Atresie Hufnagel-Klappen, die haufiger sind, wurden der Liste hinzugefügt Aorten-Aneurysmen, die bis zu Lancisi zurückgehen, kamen hinzu, Thoraxverformung, Myxom des linken Herzohres, Ruptur ierte Sehnenfaden, Pneumoperitoneum und eine tonende Milz haben die Liste anschwellen lassen Unsere Kenntnis der ratselhaften Verflochtenheiten der klinischen Medizin wachst mit wahrgenommener Erfahrung, geschultem Verstandnis und unmittelbarer Untersuchung Wir finden nur dann heraus, was vorliegt, wenn wir jenen Teil von uns selbst aufopfern, der zu ganzlicher Aufmerksamkeit und Konzentration führt Wir sehen und hören, was vorliegt nur, wenn wir schauen, lauschen und die Richtung genau bestimmen Wir

entdecken, wonach wir forschen, nicht, wonach wir schauen

War der Geist Robert Hooke's heute abend unter uns, wurde sein Interesse an den Phanomenen der Natur einigen Ansporn gegeben haben, und vielleicht hatte er Freude behabt an meiner Antwort auf seine Frage, "Wer es erlebt, dass man die Vorgange, die in den verschiedenen Buros und Geschaften des menschlichen Korpers geschehen, an den Gerauschen erkennen kann, die sie verursachen und dadurch feststellt, welches Instrument oder Gerat in Unordnung ist" An dieser Gedachtnisehrung wurde Louis Mark, wie ich hoffe, Vergnugen gehabt und ihr zugestimmt haben Damit am Ende endlich nicht zuviel hemmende Heiterkeit Sie zu dem Gedanken veranlasse, dass der Gegenstand nicht von Wichtigkeit sei, schliesse ich in aller Demut mit einem Vers aus der Heiligen Schrift (Jeremia) 17,9) "Arglistig ist das Herz mehr als alles andere wer kann es ergrunden?"

REFERENCES

1 Bean, W B "Precordial Noises Heard at a Distance from the Chest," *J A M A*, 152 1293, 1953

2 Asher, P Personal letter

3 Bricheteau "Observation d'hydro-pneumo-pericarde, accompagnée d'un bruit de fluctuation perceptible a l'oreille," *Arch Gen Med* 4th series, 4 334, 1844

4 Rees, W A and Hughes, G S "Wounds of the Chest as seen at an Advanced Operating Centre," *Lancet*, 1 55, 1918

5 Munden, W P H "Memoranda," *Brit Med J*, 1 174, 1918

6 Scadding, J G and Wood, P "Systolic Clicks Due to Left-Sided Pneumothorax," *Lancet*, 2 1208, 1939

7 Hamman, L "Spontaneous Interstitial Emphysema of the Lungs," *Trans Assoc Am Physicians*, 52 311, 1937 (The classic paper)

8 Pinckney, M M "Mediastinal Emphysema and Idiopathic Spontaneous Pneumothorax," *Va Med Mo*, 68 315, 1941

9 Curtin, R G "Cardio-esophageal Gush and Click," *Med News*, 75 330, 1889

10 January, L Personal communication

11 Greene, J A "Unusual Sounds Emanating from the Chest," *Arch Int Med*, 71 410, 1943

12 Allan, F N "Heart Noises," *New England J Med*, 218 655, 1938

13 Cottrell, J E "Personal Communication and Reference to Translation of Nicolas Tulp's Observation" This Also Appears in an Article by Sailer, J "Pulsating Spleen in Aortic Insufficiency," *Am Heart J*, 3 447, 1928

14 Fisher, W Letter and case abstract

15 James, W B "Pneumopericardium," *Trans Assoc Am Physicians*, 19 351, 1904

16 Walshe quoted by James

17 Burns, A *Observations on Some of the Most Frequent and Important Diseases of the Heart* Pp 187-189 Thomas Bryce, Edinburgh, 1809

18 Stokes, W *Diseases of the Heart and the Aorta* Lindsay & Blakiston, Philadelphia, pp 37, 1855

19 Cottrell, J E Personal communication

20 Pepper, O H P "Magnified Heart Sounds Due to Extracardiac Conditions with Report of an Unusual Case," *J A M A*, 58 340, 1912

21 Howard, C P "Aortic Insufficiency Due to Rupture by Strain of a Normal Aortic Valve," *Canad Med J*, 19 12, 1928 Comprehensive and detailed study with many gleanings from forgotten and out of the way reports Source for most subsequent reviews

22 Royster, H A Personal letter

23 Bellet, S, Gouley, B, Nichols, C F and McMillan, T M "Loud Musical Diastolic Murmurs of Aortic Insufficiency," *Am. Heart J*, 18 483, 1939

24 Editorial "Intracranial Bruits," *Lancet*, 1 239, 1956

25 Taylor, F R Personal letter

26 Purves, G H "Whistling Noise Over the Temporal Area," *J A M A*, 152 774, 1953
27 Wilcox, M B "A Bruit in the Left Ear," *J A M A*, 153 1231, 1953
28 Laennec, R T H De l'auscultation mediate, Brosson et Chaudé, Paris, 1819 Forbes Translation of Ed 3, Samuel and William Wood, N Y, 1838
29 Frost, J and Bing, J "Some Cases of Precordial Sounds Audible at a Distance," *Acta Med Scand*, 105 411, 1940
30 Warburg, E "Cardiac Murmurs Audible At-a-Distance—Mitral Stenosis Thrombosis in the Right Ventricle, Pulmonary Infarction," *Acta Med Scand*, 107 503, 1941
31 Levine, S A and Harvey, W P *Clinical Auscultation of the Heart* W B Saunders Co, Philadelphia & London, 1949
32 Eidsmoe, N A Personal communication
33 Tjalma, R A Personal communication
34 Wild, J and Bean, W B Unpublished observations
35 Dock, W *Heart Sounds, Cardiac Pulsation, Coronary Artery Disease* The Porter Lecture U of Kansas Press, 1956
36 Calo, A I soffi extra-cardiaci diastolici A proposito di un soffio cardio-polmonare musicale udibile a distanza Reggio Emilia Poligrafica Reggiana, 1952
37 Palfrey, F W "A Case of Chronic Infective Endocarditis with Ulceration of Chordae Tendineae," *Boston Med and Surg J*, 167 55, 1912
38 Love, J K "Case of Hydro-Pneumopericarditis," *Lancet*, 1 319, 1888
39 Bubis, J L "Acute Pericarditis Following the Removal of Gonorrheal Pyosalpinx," *Cleveland Med J*, December, 1908
40 Young, R D and Hunter, W C "Primary Myxoma of the Left Ventricle with Embolic Occlusion of the Abdominal Aorta and Renal Arteries," *Arch Path*, 43 86, 1947
41 Duboczky, B O "Loud Millwheel Murmur Presumably Caused by Air Embolism In a Patient with Pneumoperitoneum," *Am Rev Tubere*, 70 1092, 1954
42 Bourne, G "Clicking Pneumothorax Simulating Myocardial Infarction," *Lancet*, 1 1122, 1957

Developments in the Therapy of Hypertension

An increasing number of reports over the past two years, indicate that blood pressure elevation which is adequately severe and which exists for a prolonged period of time, will produce progressive vascular in the brain, the heart, and the kidneys The more severe the hypertension, the more marked these changes will be Observations made on renal function in hypertensive patients indicate that effective reduction in the blood pressure may completely arrest these vascular changes in the kidneys regardless of the method used for blood pressure reduction Although the vascular changes are arrested, function rarely returns to normal

Hypertension aggravates and hastens the development of arteriosclerosis Reducing the blood pressure arrests this hastening process, but still arteriosclerosis progresses just as it does in the normotensive individual The method of blood pressure reduction here too is probably not important Sympathectomy is effective in reducing the blood pressure when concurrent medical therapy is used in those patients who do not respond to sympathectomy alone There is no serious objection to this approach just as long as the blood pressure is severe enough to warrant surgical therapy and the surgeon is proficient at doing sympathectomies On the other hand, when the psychiatrist, or the generalist, or the internist who carries psychiatric overtones, can talk the blood pressure down, this is good therapy Unfortunately this is rarely possible in the patient who has a diastolic hypertension which is fixed, especially when the diastolic pressure is fixed above 120 mm Hg

Any drug therapy that is effective in bringing the blood pressure to a normal or relatively normal level, is an effective therapeutic program Generally speaking, the most effective therapeutic program has been one of polypharmacy, in which an attempt is made to deplete body sodium with Chlorothiazide (Diuril) Then, drugs are given which depress the sympathetic nervous system The centrally acting drugs are used first The most common ones are Rauwolfia and hydralazine (Apresoline) Usually in milder cases Rauwolfia is recommended and if the patient needs additional therapy, hydralazine may be added In the more severe cases, a therapeutic trial of hydralazine with rauwolfia may be employed, but when the diastolic blood pressure is fixed above 120 to 130 mm Hg, ganglionic blocking agents must usually be given for adequate control

An effective program of drug therapy is to start the patient on 500 to 1,000 mg of chlorothiazide twice a day After one week, Rauwolfia (Alseroxylon) is given in addition to the chlorothiazide starting with a dose of 8 mg (4 tablets) a day After two weeks the dose of Alseroxylon

TABLE I

THERAPEUTIC APPROACH TO THE PATIENT WITH HYPERTENSION

Severity of Hypertension	Initial Therapy	Adjunctive Therapy*
Systolic blood pressure elevation diastolic blood pressure <100 mg Hg	None	None
Diastolic blood pressure >100 mm Hg but <120 mm Hg	Chlorothiazide	Rauwolfia or Rauwolfia + hydralazine
Diastolic blood pressure >120 mm Hg	Chlorothiazide + Rauwolfia	Hydralazine or ganglion blocking agent
Severe progressive hypertension	Chlorothiazide + Rauwolfia	Ganglion blocking agent†

*Adjunctive therapeutic agent to be added to regimen if initial therapeutic agent is found to be inadequate alone

†Must be added without delay when indicated

is reduced to 4 mg per day This regimen is then continued for approximately one month in mild to moderately severe disease to test for maximum responsiveness When the response is not adequate hydralazine can be added, starting with a dose of 25 mg after each meal and at bedtime but the doses should be given at least four hours apart The does is increased in 25 mg increments until a maximum of 600 mg per day is given When the patient is not responsive to this drug, it should be discontinued in preference for a more effective drug Because of the potential side effects, hydralazine should not be continued when it fails to produce the desired therapeutic results

Patients with severe disease, particularly those with papilledema will usually require the administration of a ganglionic blocking agent in addition to the Chlorothiazide and rauwolfia There are some points of importance to note when the use of ganglionic blocking agents is anticipated The first problem is effective dose titration It is highly important to start with a small dose of the ganglionic blocking agent, gradually increasing the dose until the standing pressure reaches the desired level, usually about 150/100 The therapist should use not only blood pressure observations in the office, but also use symptomatology to arrive at the proper dose If the patient comes in and says he has attacks of dizziness at certain times during the day, this is adequate to show that he is getting excessive hypotension at that time Using symptoms plus the blood pressure observations (using home blood pressures in some patients) regulation of blood pressure is less difficult When Pentolinium (Ansolysen) is used, the initial dose of the blocking agent is 20 mgm taken after breakfast and supper The dose is increased in 20 mgm increments at weekly intervals until the standing blood pressure reaches the desirable levels When Mecamylamine (Inversine) is used it is started at a dose of 2½ mg at breakfast and supper, followed by giving a daily lunch dose of 2½ mg

After one week the lunch dose is gradually increased, then the breakfast dose is increased and so on The supper dose trails behind Because the drug action lasts a long period of time, the patient should receive the biggest doses in the morning, and at lunch since at night when he is relaxed, he does not need nearly as much drug If a large dose is taken at night, when the patient gets up in the morning after a period of relaxation, he may experience excessive hypotension

In using ganglionic blocking agents, it is usually a good idea to use them in combination with Rauwolfia, because the combination not only blocks the sympathetic nervous system, in the brain, and at the ganglia simultaneously but in addition the sedation and tranquility from the Rauwolfia compound is obtained

The problem of constipation This is an ever present problem associated with the use of ganglionic blocking agents because not only are the sympathetic ganglia blocked with these compounds but also the parasympathetic ganglia are blocked which results in constipation The therapist must be very vigilant against constipation, and use cathartics freely The cathartic of choice is a matter of trial and error Cascara is probably the best There are a number of compounds available in tablet form, such as Dorbane The elixir of Cascara Sagrada is likewise very effective Some patients do not do so well with cathartics, and will do much better with Prostigmine in a dose of 15 to 30 mg about an hour before breakfast On the other hand, some patients get rather severe cramps with Prostigmine and do better with the cathartics The therapist must find by trial and error which is the best for the individual patient At the beginning of the treatment, it is difficult to arrive at the precise method of therapy for any one particular patient

Renal Damage When renal function is depressed due to advanced damage to his kidneys, the kidneys are not able to adjust when the blood pressure is reduced too rapidly or excessively because of the vascular spasticity If the kidneys are already functioning poorly because of the vascular damage, bringing the blood pressure down may actually temporarily enchance existing renal failure However, when the blood pressure is controlled for a prolonged period of time, progressive vascular changes are arrested Therefore, in the patient who has an elevation in the BUN, the therapist should probably not reduce the blood pressure to the normotensive level immediately After a month of blood pressure regulation, he can usually adjust it without functional depression When the BUN is normal before treatment, the blood pressure can be reduced to normotensive ranges without worry If the blood urea nitrogen is 30 to 60 mg per cent usually the blood pressure in the standing position should not be reduced below 170 systolic and 110 diastolic When the BUN is 60 to 100 mg per cent, the blood pressure should not be reduced much below 190/120 initially Then after the pressure is regulated at this level for two to four weeks, it can gradually be brought to normotensive levels without further aggravating the renal failure When the BUN is more than 100, it is hopeless unless they have concomittant heart failure The mortality in our patients, when

the blood urea nitrogen was more than 100 mg per cent was 100 per cent, and we have not helped the patient by reducing the blood pressure, this again indicates that it is best to treat the patient before the vascular damage has progressed beyond the point of no return

Finally unless the therapist finds means and methods for stabilizing his patient as far as his reactions to his environment are concerned, he is going to have a pretty difficult problem regulating doses of the drugs, because the drug is used at a fixed dose, which is not nearly as effective as the hemostatic body mechanism would be under normal conditions So again, there are definite limitations to the drug therapy of hypertension

JOHN H MOYER, M D *
Philadelphia, Pennsylvania

*Professor of Medicine, Department of Internal Medicine, Hahnemann Medical College and Hospital

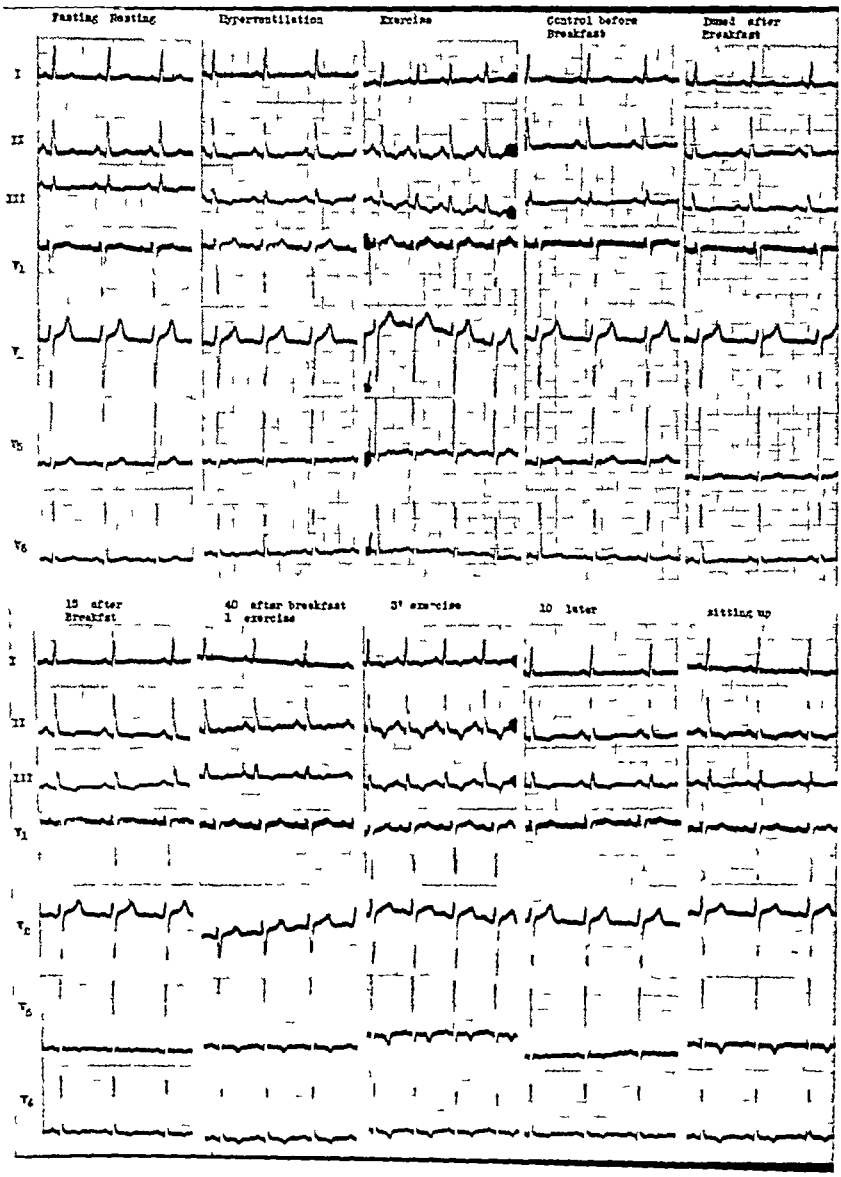
THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanations offered

---

During the examination of a 33 year old man who had applied for a position as an airplane pilot an electrocardiogram was encountered that showed small inverted T waves in the left precordial leads There was no history and no other signs that suggested heart disease In an attempt to investigate the electrocardiogram more fully records were made as shown in figure 1

It is to be noted that the electrocardiogram made under basal conditions is entirely within normal limits When hyperventilation and exercise are performed by the fasting patient the T waves in Leads II, V5 and V6 became inverted but returned to their basal form within a short period of time (see "control before



breakfast") Not immediately following a meal, but fifteen minutes later there are T wave changes in Leads II, V5 and V6 that remain constant for more than forty minutes Hyperventilation and exercise produce more marked effects now than they did while fasting Additionally, three minutes of vigorous bicycle exercise results in inversion of the T wave in Lead I Ten minutes later this effect is gone, the tracing having largely returned to the form that resulted from food alone Both in the limb leads and precordial leads the T waves could be inverted by having the patient sit up

There was no history suggesting a cardiac lesion and the physical examination and X-ray studies revealed no evidence of heart disease of any kind

The electrocardiographic study shows, in general, T wave changes that we found to be common among young healthy adults 18-28 years of age Lowering and inversion of T waves in Leads with large R waves result from increasing rate, exercise, and other non-pathologic conditions that diminish the magnitude of the ventricular gradient The inversion of the T wave in Lead I that occurs in this case will attract much attention There is sound basis for concluding that the T wave may occasionally be inverted in Lead I in the absence of disease especially in the circumstances under which it is encountered here However, the incidence of this finding among normals under ordinary circumstances is so small that it is bound to be held suspect under any circumstances

We believe that the inversion of the T waves in this case, occurring under the circumstances indicated, are probably not produced by disease We base our conclusion upon the confidence that we have in the physiologic approach to electrocardiographic interpretation In order to record an opinion that an inverted T wave in Lead I may be normal we recognize that it is necessary to overcome a rather deep-rooted prejudice that grows in the soil of the statistical approach to the limitations of normal variations Since the statistical approach has been so confusing in relation to so many electrocardiographic problems it is perhaps time to uproot some of the prejudices that have grown out of it

Unfortunately, as so often occurs, we can not be absolutely certain that our conclusion in this case is correct, for an antero-lateral zone of epicardial ischemia can also diminish the magnitude of the ventricular gradient and thus cause similar inversion of the T waves However, when ischemia is responsible for small inverted T waves, exercise will generally cause the T waves to become upright again On the other hand, if the diseased area of myocardium is represented by scar tissue, with little or no surrounding ischemic zone, the electrocardiogram may well behave as it has in this case In the latter case QRS changes that reveal the presence of such scarring may not be discernible

MANUEL GARDBERG, M D and IRVING L ROSEN, M D*
New Orleans, Louisiana

*From the Cardiac Research Laboratory, Touro Infirmary and the Department of Medicine, Louisiana State University Medical School

Case Report Section

Cardiac Dysfunction in Severe Hyperkalemia*

LAWRENCE H GOLDEN, M D , F C C P **

New Orleans, Louisiana

The clinical manifestations of hyperpotassemia are well described in the current literature, and the electrocardiogram is one of the most important diagnostic aids in establishing this syndrome This paper is primarily concerned with the management of the often dramatic electrocardiographic abnormalities seen in patients with hyperkalemia

The electrocardiograph was first used to demonstrate the effects of abnormal serum levels of potassium in the animal laboratory in 1938 by Winkler [1] and again by Chamberlain [2] in 1939 Since that time many investigators [3-7] have described similar alterations in the electrocardiograms of human beings with hyperpotassemia

The progressive electrocardiographic changes seen with rising serum potassium have been summarized by Burch and Windsor [8] as follows

1 Increased magnitude of T waves
2 Depression of the ST segment
3 Disappearance of U waves
4 Increased duration of the QRS complex
5 Increased PR interval
6 Distortion of P wave with a decrease in magnitude
7 Prolongation of QRS to produce a pattern of bundle branch block
8 Auricular standstill
9. Ventricular fibrillation

The most characteristic change seen in peaking of T waves and increase in the duration of the QRS complex

Attempts at correlation between serum levels of potassium and electrocardiographic alteration are difficult, since it is the intracellular potassium which is important in determining the cardiac muscle response Taiail [9] pointed out that with serum levels of 6 8-7 6 mEq/liter, the electrocardiogram showed inconstant changes, but when the serum level was over 7 8 mEq/liter, the changes were consistently present

The following case of acute glomerulonephritis demonstrates many of the typical abnormal electrocardiographic features of hyperkalemia

The patient was an 18 year old airman who had streptococcal pharyngitis in October, 1955 which was treated with penicillin Early in November, 1955, he had recurrent sore throat but did not seek medical attention In December he was hospitalized with complaints of pain and swelling of both knees and wrists and a rash on the lower legs Past history was negative

*From the 3650th Air Force Hospital, Sampson A F B Geneva, New York

**Tulane University School of Medicine, Department of Medicine, New Orleans, Louisiana

Physical examination revealed an acutely ill, well developed, well nourished man Blood pressure was 115/70, temperature 99 8° F , pulse 92, respirations 20 The examination of the head, including eyes, ears, nose, and throat, was negative except for slight infection of the pharynx His neck was supple and his chest and lungs normal The heart rhythm was regular and a grade I systolic murmur was heard at the apex There was no palpable thrill or friction rub heard The pulmonic second sound was slightly accentuated The abdomen, back and genitalia were normal The joints and extremities exhibited slight swelling of ankles but no erythema or increase in temperature was noted Extensive purpuric lesions were present over both lower extremities

On admission the white blood cell count was 15,000 with 82 polymorphonuclear leukocytes, hematocrit 45 per cent, sedimentation rate 36 mm per hour The urine was negative for sugar, albumin, and microscopic findings A chest x-ray film and electrocardiogram were normal A throat culture was negative for Beta hemolytic streptococcus Platelet count, bleeding and clotting time, clot retraction, prothrombin time, and capillary fragility tests were all normal

In the first month, the illness was that of the rheumatic state The laboratory and electrocardiographic studies gave confirmation of active myocarditis During this

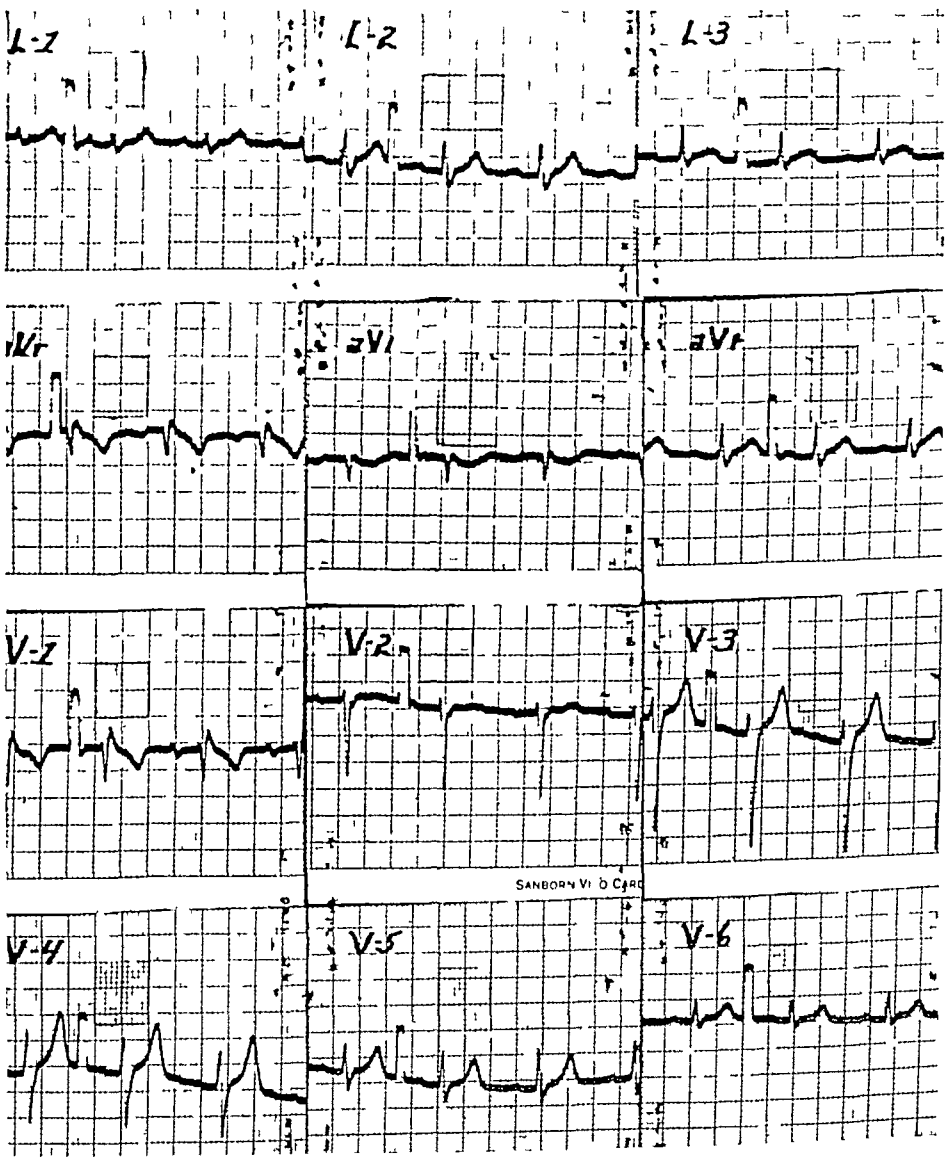


FIGURE 1 Base line electrocardiogram Low voltage is present in Lead I The auricular and ventricular conduction times are normal The voltage and form of the T waves were considered to be within normal limits

time abdominal pain was a frequent complaint Radiographic studies of the gastrointestinal tract were not helpful The arthritis and purpura gradually cleared but fever persisted

In the fifth week of hospitalization the urine exhibited microscopic red blood cells, albumin and casts During the course of the next week, he developed pleural effusion, weight gain of 20 pounds, peripheral edema, and elevation of blood pressure to 160/100 The laboratory findings demonstrated early uremia and mild acidosis A urine culture showed the presence of Escherichia coli, and he was treated effectively for this with chloromycetin

The disease progressed, and with the urine output gradually dropping, he became more uremic and acidotic The urea nitrogen was 60 mg per cent, hematocrit 30 per cent, CO_2 combining power 41 vol per cent A supportive regimen including restricted salt intake, digitalization, and small blood transfusions was carried out, without improvement

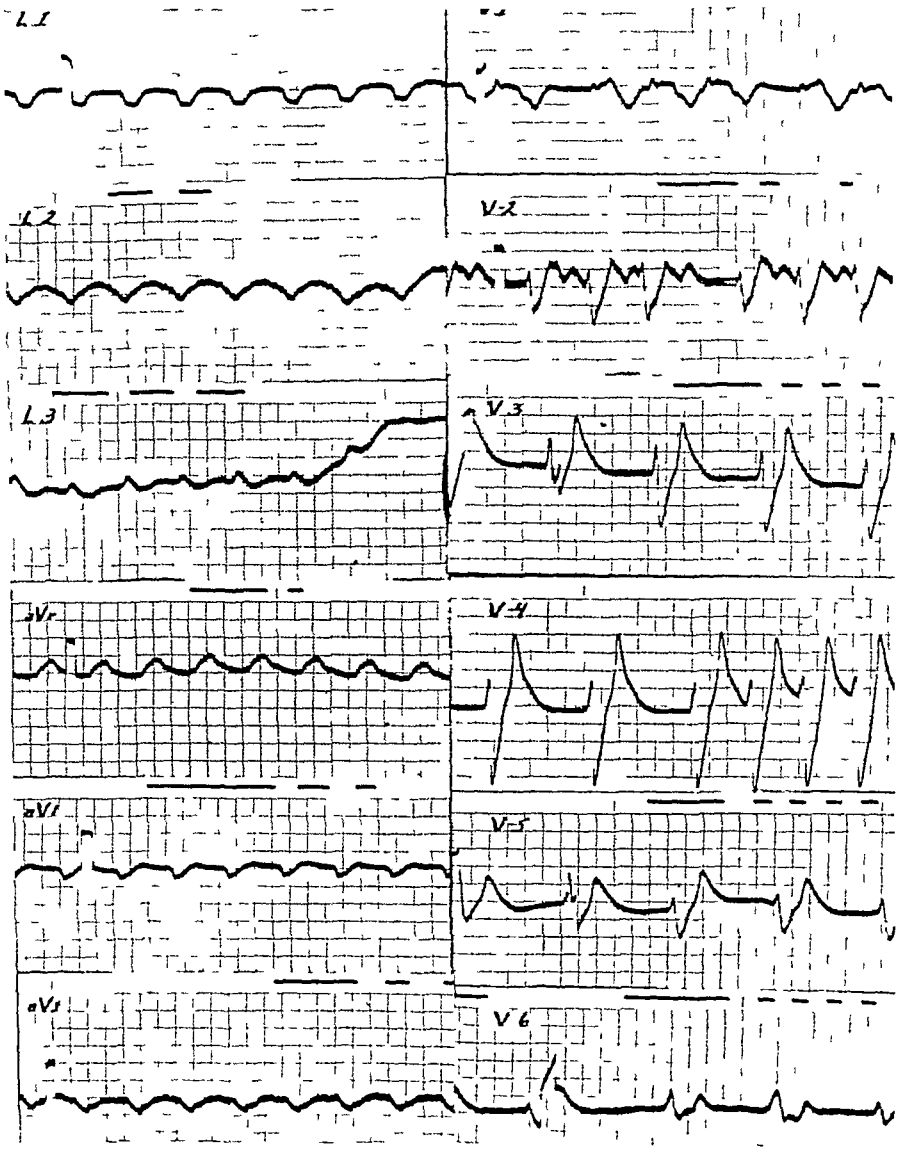


FIGURE 2 Serum potassium recorded 8 6 mEq /liter at this time Electrocardiogram exhibiting peaked T waves, diminution of the R wave A-V dissociation with widening of the QRS, depression of ST segment and merging of the QRS and T waves into a sine wave

At the end of the eighth week of hospitalization, the serum potassium rose to 7.0 mEq./liter. The use of retention enemas with potassium-removing resins effected temporary reduction to 6.4 mg. On February 13 and again on February 22, he was dialyzed by Dr. Arthur MacNeill and staff of the University of Buffalo, using the MacNeill Mark XI-b dialyzer.[15] The second dialysis produced a good chemical response with the blood urea nitrogen dropping from 170 mg. per cent to 90 mg. per cent. Subjectively he was improved, though renal function remained severely impaired.

On March 3, he developed acute hyperkalemia with serum potassium of 8.6 mEq./liter. Clinically this was manifested by Cheyne-Stokes respirations, marked lethargy and diamatic alteration of the electrocardiogram. Figure 1 shows the electrocardiogram taken on December 29, 1955. At this time regular sinus rhythm was present with normal auricular and ventricular conduction times. The T waves are not considered grossly abnormal and electrolyte imbalance is as yet not evident from our laboratory procedures. Figure 2 shows the electrocardiogram at the time of the increase in serum

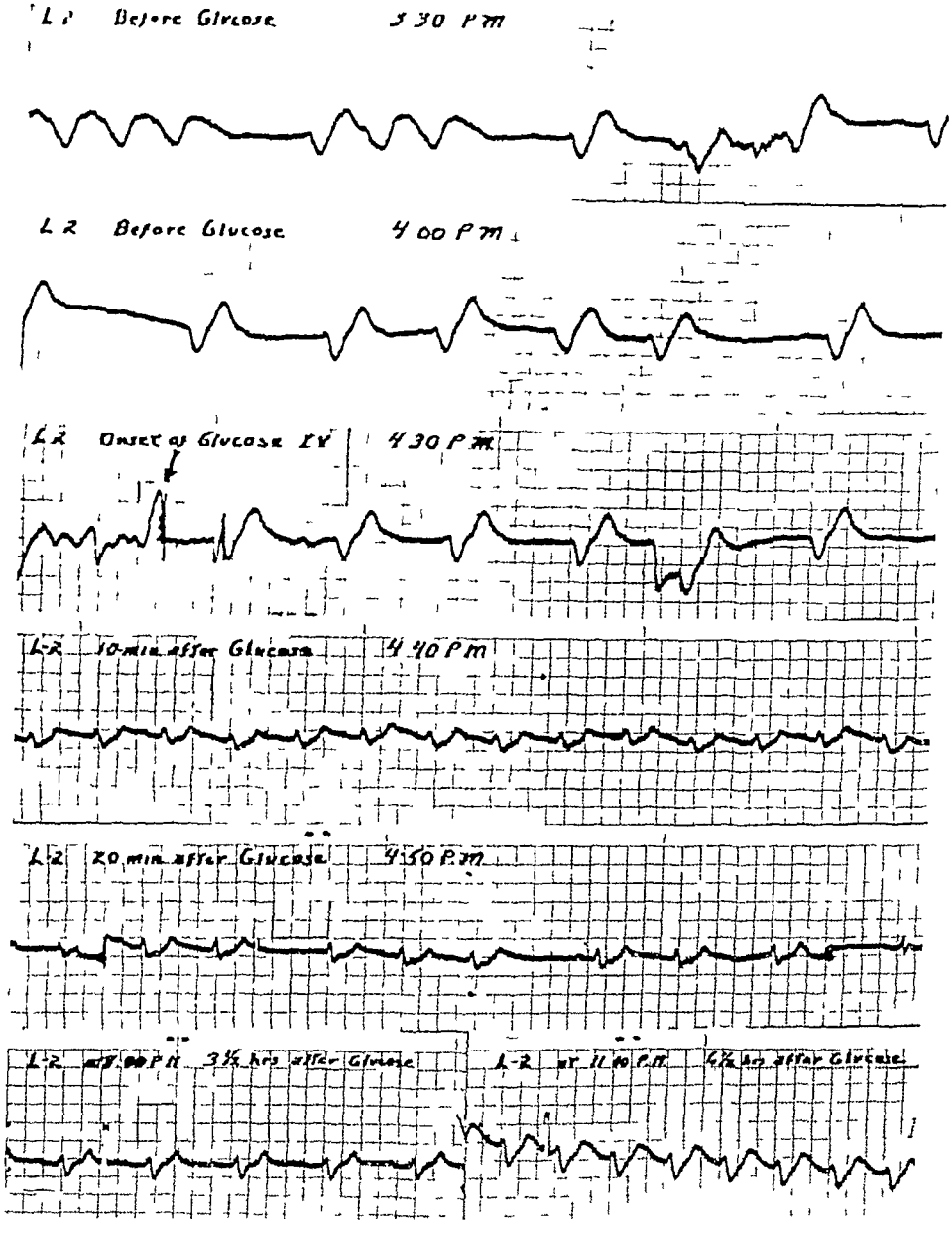


FIGURE 3. The progressive response to intravenous glucose and insulin at the time. The fourth and fifth strips show A-V dissociation with more normal ventricular complexes. Sinus mechanism was established after three and one-half hours of glucose and insulin administration.

potassium Peaked T waves are noted in V3 and V4, the diminution of R wave, absence of P wave, widening of the QRS complex, and merging of the QRS and T into a sine wave, are all demonstrated at this time Figure 3 shows short sections of Lead II before 1,000 cc of 10 percent glucose and 40 units of regular insulin were administered, and then at 10 minutes, 20 minutes, three and one-half hours, and six and one-half hours after the start of glucose administration The reversion to normal rhythm is demonstrated in the electrocardiogram taken the following day (Figure 4), but voltage is considerably reduced On March 6, 1956, the electrocardiogram was very near in appearance to the one prior to the abrupt rise in serum potassium Because of the persistence of uremia and anuria, dialysis was again performed on March 6, 1956 The procedure was tolerated well, even though severe acidosis was present Four hours after termination of the dialysis the patient convulsed, and in the next 10 hours he had 20 more convulsions The blood pressure rose to 210/100 Magnesium sulfate, heavy intravenous sedation, and hypertonic fluids were used without response, and he expired on March 7, 1956 Post mortem examination demonstrated the renal findings seen with acute glomerulonephritis

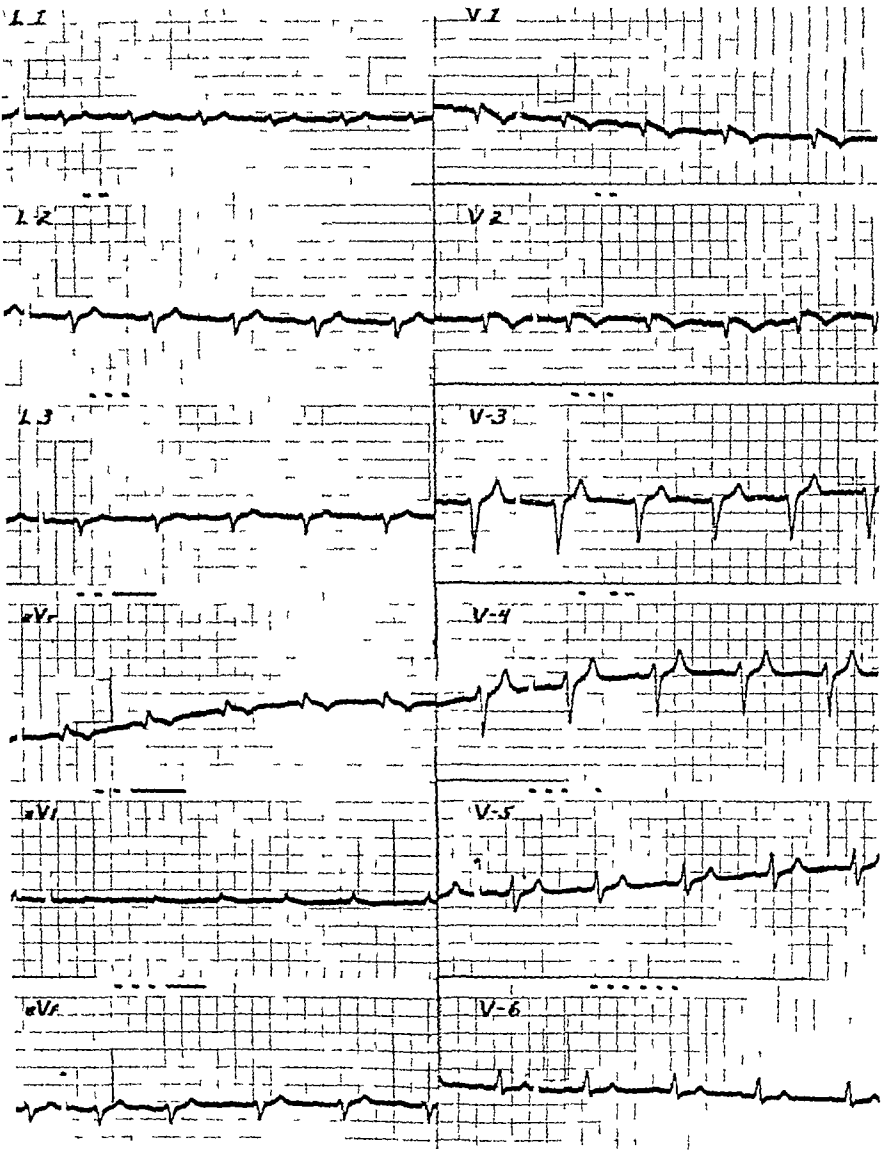


FIGURE 4 Tracing taken on succeeding day Persistence of sinus mechanism with delayed A-V conduction and low voltage

Treatment Differential

The management of this case presented several problems, of which the control of hyperkalemia is frequently the most difficult Unfortunately, there is no specific treatment for the primary pathology in acute glomerulonephritis, but the complications of uremia, acidosis, and hyperkalemia which produce the fatality can frequently be controlled

The aim of current therapy is to forestall these complications while waiting for the kidney to resume its normal functions Finch,[10] Merloney,[11] and their associates demonstrated that temporary lowering in serum potassium can be accomplished by the use of simple physiological saline solution They point out that the addition of calcium, particularly when serum levels of this ion are concomitantly depressed, further aids by directly antagonizing the effects of potassium on the heart muscle Danowski[12] and Elkinton[13] report the successful reduction of serum potassium through the use of cation exchange resins Employment of various dialysis techniques has been demonstrated by Kolff[14] In our case the MacNeill blood dialyzer,[15] which is of unique design and highly effective function, was used in the later stages of the illness

Recently the use of carbonic anhydrase has been described by Mosely[16] The resultant decrease of available hydrogen ion without blockage of potassium ion transfer from intracellular position in the renal tubules to the tubule lumen, increases potassium excretion in the urine The favorable response of patients with hyperpotassemia to exchange transfusion technique has been reported by Goldbloom[17]

Bellet and associates[18] have shown the effectiveness of molar sodium lactate in the control of heart block secondary to hyperkalemia as well as to other etiologies The mechanism of action is still under investigation The current concept is that return of abnormal electrolyte patterns to a more physiological state results in an increase in cardiac rhythmicity

The use of hypertonic glucose and insulin was initially demonstrated by Darrow[19] and again more recently by Goldbloom[17] The net effect is the deposition of glycogen similar to that occurring in the treatment of diabetic acidosis Concurrently potassium is transferred into the cell at a rate that Darrow[19] estimated at 0 36 millimoles of potassium per gram of glycogen The insulin acts to stimulate the deposition of glycogen, though it is not considered to have a specific potassium reducing effect in itself The latter form of therapy was used to correct the cardiac arrhythmias in this case

REFERENCES

1 Winkler, A W, Hoff, H E and Smith, P K "Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride," *Am J Physiol*, 124 478, 1938

2 Chamberlain, F L, Scudder, J and Zwemer, R "Electrocardiographic Changes Associated with Experimental Alterations in Blood Potassium in Cat," *Am Heart J*, 18 458, 1939

3 Levine, H D, Merrill, J P and Somerville, W "Disturbance of Cardiac Mechanism in Potassium Intoxication," *Circulation*, 3 889, 1951

4 Herndon, R F, Meroney, W H and Pearson, C M "The Electrocardiographic Effects of Alterations in Concentration of Plasma Chemicals," *Am Heart J*, 50 188, 1955

5 Cullens, J H and Crawford, J D "The Electrocardiogram and Disturbances of Potassium Metabolism," *New England J Med*, 243 843, 1950

6 Steward, H F, Sheppard, E M and Horger, E L "Electrocardiographic Manifestations of Potassium Intoxication," *Am J Med*, 6 828, 1948

7 Keith, N M, Burchell, H B and Baggenstoss, A N "Electrocardiographic Changes in Uremia Associated with High Concentration of Serum Potassium," *Am Heart J*, 27 817, 1944

8 Burch, G E and Windsor, T *A Primer of Electrocardiography*, Lea and Febiger, 1956

9 Tarail, R "Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances," *Am J Med*, 5 828, 1948

10 Finch, C A, Sawyer, C G and Flynn, J J "The Clinical Syndrome of Potassium Intoxication," *Am J Med*, 1 337, 1946

11 Meroney, W H and Herndon, R F "The Management of Acute Renal Insufficiency," *J A M A*, 155 877, 1954

12 Danowski, T S, et al "The Use of Cation Exchange Resins in Clinical Situations," *Ann Int Med*, 35 529, 1951

13 Elkinton, J R "Treatment of Potassium Retention in Uremia with Cation Exchange Resins," *Am J Med Sc*, 220 547, 1950

14 Kolff, W J "Serum Potassium in Uremia," *J Lab Clin Med*, 36 727, 1950

15 MacNeill, A E, Doyle, J E, Witebsky, E and Swanson, P R "Unusual Hemolytic Transfusion Reaction with Renal Failure Treated by Hemodialysis," *J A M A*, 161 1630, 1956

16 Mosely, V "The Use of Carbonic Anhydrase Inhibitor in the Treatment of Hyperkalemia," *J Am Geriat Soc*, 4 58, 1956

17 Goldbloom, R B "Renal Failure with Extreme Hyperpotassemia," *New England J Med*, 250 717, 1954

18 Bellet, S and Wasserman, T "Indications and Contraindications for the Use of Molar Sodium Lactate," *Circulation*, 15 591, 1957

19 Darrow, S C "Blood Fluid Physiology Role of Potassium in Clinical Disturbance of Body Water and Electrolyte," *New England J Med*, 242 1014, 1950

A Large Pseudoaneurysm Caused by Extrapleural Plastic Ball Plombage

MASASHICHI KAWANO, M D , F C C P , SOROKU SAHEKI, M D *
and YUZABURO MURATA, M D **
Nagasaki, Japan

Collapse therapy of pulmonary tuberculosis by means of plastic plombage is now out of use except in a few clinics or with radical modification Reasons for this abandonment are a series of complications some of which have led the patients to unhappy outcomes We have recently met with one of these situations and thought it worthwhile to report it here

Clinical History The patient was a 32-year-old man who had been diagnosed as having a tuberculous lesion in his left upper lobe in 1949 and underwent collapse surgery using several plastic balls of larger size at the University Hospital on December 27, 1949 He had not noticed subjective symptoms until July 20, 1956, when he felt a sudden pain and pressure inside his left chest wall after elevation of his left arm Slight fever, and coughing, without expectoration, lasted for a few days but no pulmonary hemorrhage, or blood-streaked sputum, was noticed He visited our hospital asking for removal of the plastic balls We hesitated to operate on him immediately and watched him carefully, for the fever between 99 and 101° F persisted for a long period While we were still pondering on the indication of removal of plastic balls in this condition, hemoptysis started on August 8, 1956 and within a few days it changed into a profuse hemorrhage exceeding 500 cc on the night of August 25th The hemorrhage reached 1,000 cc the next night and he complained of a severe chest pain which was *hardly controlable by injection of large doses of* demerol, and he requested immediate thoracotomy and removal of the balls

Operation He was subjected to thoracotomy on August 31, 1956 To combat the pulmonary hemorrhage during operation, he was placed in the face-down position, using the table specially built for this purpose For the same reason regional anesthesia was preferred to general anesthesia, in which preservation of tracheal reflex and maintainance of air-way is a hazardous problem The regional anesthesia was reinforced by intramuscular administration of M_1 cocktail consisting of Chlorpromazine 50 mg, Demeral 105 mg and Prometazine 50 mg one hour prior to operation

Three ribs, third, fourth and fifth, were resected following skin incision and division of muscles Then the thorax was entered through the 5th periosteal bed Adhesion of the lung to the wall was so severe that detachment required a meticulous manipulation The lower lobe was almost intact but the upper lobe was compressed to the wall by the pressure from inside When the hematoma at the lateral edge of the upper lobe was partly removed oozing of blood was met and a gauze pack was placed to control the oozing The medial-posterior approach was taken next and the thick white pleura at the upper end of the compact upper lobe was incised Before long a part of a ball surface was disclosed and the ball was extracted with a large clamp No sooner than the removal, a torrent of arterial blood filled the chest The operator quickly probed the upper space and floating balls were all extracted in a moment A large amount of gauze packing was placed in the chest to control the bleeding, and the wound was closed in layers with interrupted silk sutures without delay The blood loss was at this time 2,000 cc, systolic pressure around 40 mg Hg, and the patient was unconscious Treatment with generous transfusion of bank blood and fresh blood, and administration of vasospastics and other drugs helped the patient to overcome the shock stage, and he survived

The second operation was undertaken a week later This time the patient was put under general anesthesia with intratracheal intubation, for absence of pulmonary hemorrhage during operation and postoperative days convinced the anesthetist of the safety of this method We presumed that the bleeding point was in the upper pulmonary vessels The chest was reopened through the old wound and without removing the gauze pack the lower lobe was mobilized to ease the intrathoracic

*From the Department of Surgery (Director Prof Hideo Tsujimura), Nagasaki University School of Medicine
**From the Department of Radiology (Director Prof Hiroshi Tachiiri), Nagasaki University School of Medicine

maneuver Then, the hilum was approached from behind The upper bronchus was exposed and treated after Sweet's method Dissection of individual vessels seemed difficult, and the remaining hilum structure was ligated together temporarily and the gauze pack was removed one after one Another massive bleeding of arterial blood succeeded the procedure and further operation was abandoned The patient again survived the operation but blood seepage from the wound persisted amounting to over 400 cc a day

Angiography To identify the bleeding point, the patient had an angiocardiogram done by the Department of Radiology The reported findings were as follows

"The angiogram taken immediately after injection of 76% Urographine 50 cc through the right saphenous vein reveals no abnormal finding in the right atrium and ventricle, although the trachea, vena cava, and heart are tracted to the right, and posterior portion of the left upper ribs were absent Lack of filling in the left upper artery is likely due to ligature of the artery at the previous operation

Angiogram taken four seconds after the injection (Fig 2) also shows no abnormal findings of the left atrium and ventricle, aortic arch, ascending and descending aorta Filling of both common carotid arteries, vertebral arteries, and subclavian arteries seem to be normal, but the left subclavian artery shows insufficient contrast in comparison with the right An unusual finding is in the vault of the left thorax where lies a round or oval homogeneous shadow of clear smooth outline spreading from the upper border of the second rib to the fourth rib No leakage of the contrast agent was recognized even at the divided end of the intercostal arteries

Angiogram taken six seconds after the injection (Fig 3) shows the presence of the above-mentioned round shadow even when contrast agent in other arteries has disappeared, but this shadow also disappeared completely in 30 minutes

From these findings this round shadow is suspected to be a large aneurysm having communication with the left subclavian or common carotid artery It is a regret that the lateral angiogram was not available because of difficulties with the apparatus and patient But it can be learned from the postero-lateral film that the aneurysm had arisen from the subclavian artery which is not filled so well as the common carotid artery The hemorrhage in patient's history is attributable to this aneurysm which shows homogeneous, smooth and round contour suggesting a relatively fresh aneurysm with incomplete organization"

Autopsy Three days later in the afternoon, the patient died suddenly following a severe cough and convulsion Orotracheal suction, and adrenalin injection failed to alter his course

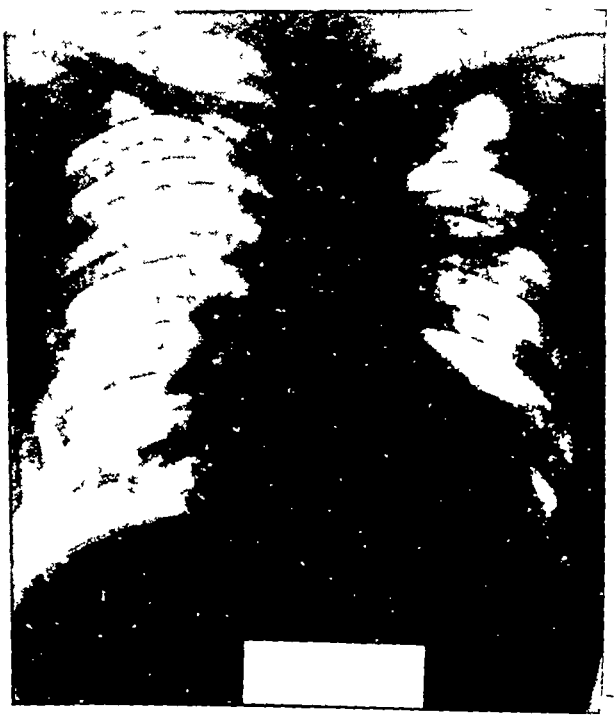


FIGURE 1 Preoperative x-ray film

Postmortem examination revealed a large sac communicating with the subclavian artery as indicated by angiograms (Fig 3) The sac was filled with blood and lined by fibrinous membrane of many layers without any vessel wall structure Apparently this is a pseudo-aneurysm formed by repetition of bleeding, and coagulation process The space between the pseudoaneurysm and the lung was filled with clotted blood, and the adjoining visceral pleura had a large defect There was found no active lesion in the upper lobe but an old partially calcified fibrous lesion No possible source of profuse hemorrhage such as cavitation or bronchial ulceration was discovered in any lobe The trachea was filled with mass of clotted blood at the lower end as were the openings of the main bronchi, and the stump of the left upper bronchus had suppurative change and was partially torn

Discussion

It is clear from the clinical and postmortem findings that the round edge of a plastic ball adjacent to the subclavian artery gave continuous pressure against the vessel wall for nearly seven years and gradually eroded the anemic necrotized wall structure and finally perforated it This was followed by bleeding which caused the chest pain and feeling of pressure, and a pseudoaneurysm had grown there But high arterial pressure did not allow the closure of the perforation and bleeding was repeated, leading to a high pressure in the collapsed space which was in contact with the pathologic lung surface, and gave the outlet for the bleeding through the bronchial route, thus causing preoperative pulmonary hemorrhage The first operation lessened the pressure in the space by removing the plastic balls The bleeding was stopped by gauze pack only temporarily We should have done an angiocardiogram on the patient before the second operation, but the condition of the patient made us hesitate to do it, and we had in mind the pulmonary vessels under the pressure of the ball as the main source of hemorrhage Thus, we operated the second time, successfully removing the upper lobe, but failed in treating the real source of bleeding This continued, or even increased following the second operation, and finally pressed into

FIGURE 2 FIGURE 3

Figure 2 Four seconds after angiographic injection *Figure 3* Six seconds after injection

the bronchial stump, which was already infected, and yielded easily to the pressure, giving way to the flow of blood into the trachea and consequent asphyxia

The most common complication of plastic plombage has been the perforation of cavity wall, and subsequent empyema Little attention has been given to the danger of perforation of important intrathoracic vessels This is unlikely to occur in a short duration after the operation but, if once started, is very difficult to control in time, unless the surgeons, as well as patients, are alert enough to find out this possible danger at an early stage

We think it is safer to remove the plastic balls as early as possible, if the balls are already in the thorax We believe plastic plombage as a treatment of pulmonary tuberculosis is an unadvisable procedure except in a few selected cases Our case teaches us that it is a necessary safeguard against severe complications to substitute for plastic plombage pulmonary resection, or thoracoplasty, even though the patient with plombage does not have any complaint

The authors wish to acknowledge the collaboration of the Department of Radiology headed by Prof Hiroshi Tachiiri and the Department of Pathology headed by Prof Shigeru Matsuoka and the suggestion and advices given by Prof Hideo Tsujimura and Assistant Prof Takashi Hirai of the Department of Surgery

BIBLIOGRAPHY

Goto, S et al "Postmortem Examination of Seven Cases Died After Extrapleural Plastic Ball Plombage," *Jap J Thoracic Surg*, 6 372, 1953
Inada, K et al "An Evaluation of Extrapleural Pneumonolysis With Filling With Plastic Balls," *J Thoracic Surg*, 27 503, 1954
Kai, Taro et al "Follow-up of 80 Cases of Extrapleural Pneumonolysis With Plastic Ball Plombage," *Jap J Thoracic Surg*, 3 341, 1950
Koshimizu, T et al "Clinical Symptoms Following Extrapleural Plastic Ball Plombage," *Jap J Thoracic Surg*, 3 212, 1950
Laird and Stephans "Plombage, Review and Report on Use of Polystan," *Tubercle*, 24 68, 1953
Lewin and Aronsvitch "Changing Indications for Collapse Therapy," *Canad M A J*, 69 481, 1953
Nagaishi, C et al "Application of Plastic for the Treatment of Pulmonary Tuberculosis and Extrapleural Pneumonolysis with Filling of Plastic Balls," *Kekkaku-Kenkyu*, 3 38, 1947
Nagaishi, C "Analytical Studies on the 'Failure' of Extrapleural Pneumonolysis with Filling of Plastic Balls," *Annals of Tuberculosis* (Jap publication), 1 No 3, 134, 1950
Sawazaki, Hiroji et al "An Evaluation of 148 Cases of Extrapleural Pneumonolysis with Plastic Ball Plombage," *Jap J Thoracic Surg*, 3 117, 1950
Sawazaki, Hiroji "Result in 1064 Cases of Extrapleural Lucite Plombage at 40 State Sanatoriums," *Iryo*, 4 95, 1950
Sawazaki, Hiroji "Plastic Resin Plombage Examined from the Standpoint of Sputum Conversion and Complications," *Jap J Thoracic Surg*, 5 8, 1952
Takatsuka, Fujio "Failures and Complications of Extrapleural Lucite Plombage," *Jap J Thoracic Surg*, 3 281, 1950
Trent, J C et al "An Evaluation of Extrapleural Pneumonolysis with Lucite Plombage," *J Thoracic Surg*, 18 175, 1948
Wilson, D A "Extrapleural Pneumonolysis with Lucite Plombage," *J Thoracic Surg*, 17 11, 1948
Woods, F M et al "Extraperiosteal Temporary Plombage in Thoracoplasty," A Preliminary Report, *Dis Chest*, 18 401, 1950
Yada, H "Complications Following Extrapleural Pneumonolysis with Plastic Ball Plombage," *Jap J Thoracic Surg*, 5 317, 1952
Yasuoka, H "Extrapleural Plombage with Plastic Balls," *Jap J Thoracic Surg*, 2 119, 1949
Yasuoka, H et al "Failures and Complications of Extrapleural Plombage with Plastic Balls," *Jap J Thoracic Surg*, 2 233, 1949

Bilateral, Primary, Simultaneous Bronchogenic Carcinoma

Presentation of a Case

E CATO DRASH, M D, F C C P and RICHARD N DE NIORD, JR, M D
Charlottesville, Virginia

The question of the multicentric versus the unicentric origin of bronchogenic carcinoma is as yet undecided Some observers believe that multiple sites of metaplastic epithelium or preinvasive carcinoma (carcinoma in situ) may exist asymptomatically throughout the bronchial tree [1 3] Auerbach has demonstrated the ubiquitous changes of hyperplasia, metaplasis and early neoplastic manifestations which appear in the pulmonary mucosa in some cases He has also shown that, in general, there are four types of metaplastic changes present in the lungs of individuals with bronchigenic carcinoma—1) basal cell hyperplasia, 2) stratification, 3) squamous metaplasia, and 4) carcinoma in situ At some point in the biological maturity of lung cancer, one of these sites attains autonomy and the atypical growth of lung cancer continues The term "bronchogenic carcinoma" used here refers to the description of Liebow[5], and includes a) epidermoid carcinoma, b) anaplastic carcinoma, and c) adenocarcinoma The alveolar cell carcinoma has a diffuse form not discussed at this time An excellent study of multiple sites of atypical bronchial epithelium was made 20 years ago by Lindbert[6] McGrath[7] has added weight to the multicentric site theory, by demonstration of multicentricity in 54 of 87 lungs containing bronchogenic carcinoma Numerous observers have described multiple pulmonary "carcinomas in situ,"[8] but few have actually visualized or described simultaneous bilateral invasive bronchogenic carcinoma Invasion signifies autonomy, and usually occurs unilaterally Because of its unusual occurrence, we are presenting one case of bilateral, primary, simultaneous bronchogenic carcinoma

This 52 year old white man was admitted to the University of Virginia Hospital with a three month history of increasing fatigability, 22 pound weight loss, cough, wheezing, and left chest pain No previous diagnostic studies had been performed prior to admission He smoked two packs of cigarettes per day for approximately 25 years Physical examination revealed diminished breath sounds over the left chest with some inspiratory wheezing and emaciation *X-ray* film demonstrated left hilar adenopathy, and a 2 cm nodule in the left apex

Discussion

Ever increasing evidence points to the multicentric origin of bronchogenic carcinoma Numerous sites of atypical metaplasia or carcinoma in situ have been repeatedly demonstrated These sites are grossly unremarkable and probably do not account for positive cytological studies [9] Besides the possibility of morphologic defects,[10] or developmental abnormalities[11] causing multicentricity, it would seem logical to assume that bronchial irritants effect the entire tracheo-bronchial mucosa and not a single re-

FIGURE 1 *Bronchoscopy—Right Side* Small one-half cm discrete, pale granular mass was present just distal to the upper lobe orifice The remainder of the right bronchial tree was negative *Left Side* A constricting, annular mass was seen in the left main stem bronchus at a level 2 cm from main carina and almost completely obstructing the lumen This lesion was also pale, discrete and bled easily on biopsy

FIGURE 2

FIGURE 3

Figures 2 and 3 Microscopic Figure 2 represents biopsy of the right and Figure 3 biopsy of the left endobronchial lesions Both lesions show typical invasive epidermoid carcinomas

stricted site Once growth and autonomy has occurred in one area, this site progresses at a variable growth rate It is interesting to note that only rarely does another area of metaplasia in the same lung (or other lung?) develop frank invasive characteristics This appears as a form of growth suppression in the remaining metaplastic areas once invasion and autonomy have occurred

REFERENCES

1 Black, H and Ackerman, L L "The importance of epidermoid carcinoma in situ in the histogenesis of carcinoma of the lung," *Am Surg*, 136 77, 1952

2 Broders, A C "Carcinoma in situ contrasted with benign penetrating epithelium," *J A M A*, 99 1070, 1932

3 Peterson, A B, Hunter, W C and Sneeden, D "Histological study of five minute pulmonary neoplasms believed to represent early bronchogenic carcinoma," *Cancer*, 2 991, 1949

4 Auerbach, Oscar et al "Changes in the bronchial epithelium in relation to smoking and cancer of the lung," *The New Eng Jour Med*, 256 97, 1957

5 Liebow, A A "Tumor of the lower respiratory tract," *Fascicle*, 17

6 Lindberg, K "Über die Histologie des primaren lungen Krebses," Arbeiten aus dem path Institut der Universitat, *Helsingfors*, 8 225, 1935

7 McGrath, E J et al "Bronchogenic carcinoma, a product of multiple sites of origin," *J Thor Surg*, 24 271, 1952

8 Ryan, Robert F, McDonald, John M "Bronchogenic carcinoma with in situ carcinoma in the opposite lung," Report of five cases Proceedings of the staff meetings of the Mayo Clinic, 31 478, 1956

9 Liebow, A A, Lindskog, G E and Blower, W D "Cytological studies of sputum and bronchial secretion in the diagnosis of cancer of the lung," *Cancer*, 1 223, 1948

10 Mulligan, E M and Harper, Fred R "The morphology of primary carcinoma of the human lung," *J Thor Surg*, 12 734, 1943

11 Womack, Nathan, A and Graham, Evarts, A "Developmental abnormalities of the lung and bronchogenic carcinoma," *Arch Path*, 34 301, 1942

Editorial

War — A Disease

Sweden is a small country and though its earlier history is full of war, it has now lived in peace for almost 150 years Our own history, like our experiences in the shadow of two World Wars, has taught us that war never pays, not even for the victor Wars lead only to new wars, with all its accompanying human suffering War is a disease, a disease not of individuals, but of countries It can be acute, flaring up quickly and soon over More often, it is chronic and spreads like a plague, constantly involving new countries and ultimately threatening—as it does now—the existence of the entire world We all know that chaos threatens, that the latest technical advances have produced weapons which can exterminate great sections of the population—even place in jeopardy the existence of every living being on this planet Everything that can be done to prevent such a development must be done—and quickly Somehow or other, nations must reach an agreement The cold war must be brought to an end and the world once more restored to peace, a true peace

All this is simple enough to say, perhaps especially so for us doctors whose mission is to heal, not to destroy To this end, we increase our knowledge, seek experience at national and international congresses and convert this knowledge into deeds We support and participate in the efforts to raise the living standards of our populace We successfully combat epidemics We detest war not only because it destroys everything that has been built with so much effort, but, above all, because of what it costs in human suffering For these reasons, we gladly participate in the Doctors' Crusade for Peace

In the campaign against war as a disease of nations, the same means have been employed as we ourselves use in our work as doctors, although naturally on a much greater scale The generous aid which the United States of America has given to underdeveloped and needy countries cannot be too highly praised It contributes to a higher living standard, provides opportunities for work and thus enhances the will to live At the same time, it increases resistance against physical and psychic infections of various kinds Of corresponding importance is the aid given to countries in their campaign against diseases Other and stronger medicines are needed, and the doctors for this are our statesmen on whom rests a heavy responsibility, all the more so as it may now be a question of life or death for every one of us We look with hope to the United Nations where all the threads meet Let us trust that success will be achieved here in solving the difficult problem of welding all nations together into unity so that the world may at last gain what it has so long yearned for—enduring peace

Erik Hedvall, M D , F C C P *
Uppsala, Sweden

*Governor of the College for Uppsala, Sweden

FIFTH INTERNATIONAL CONGRESS
ON
DISEASES OF THE CHEST

The Council on International Affairs of the American College of Chest Physicians takes pleasure in announcing the following schedule of activities in connection with the Fifth International Congress to be held in Tokyo, Japan, September 7-11, 1958 All arrangements for the Congress have been made with the cooperation and generous assistance of the College officials in Japan

Saturday, September 6

9 00 a m —Registration	DAIICHI BUILDING
10 00 a m —Opening Executive Session Regents and Governors	TOKYO KAIKAN
12 00 noon—Luncheon Meeting, Editorial Board "Diseases of the Chest"	TOKYO KAIKAN
2 00 p m —International Committee Meetings	TOKYO KAIKAN

Sunday, September 7

9 00 a m —Registration	DAIICHI BUILDING
8 30 p m —Inaugural Ceremony and Convocation	YOMIURI HALL

Monday, September 8

8 00 a m —Registration	DAIICHI BUILDING
9 00 a m —Scientific Sessions	DAIICHI BUILDING
2 00 p m —Scientific Sessions	DAIICHI BUILDING
6 00 p m —Reception by Hon Nobusuke Kishi, Prime Minister, at his official residence	

Tuesday, September 9

8 00 a m —Registration	DAIICHI BUILDING
9 00 a m —Scientific Sessions	DAIICHI BUILDING
2 00 p m —Scientific Sessions	DAIICHI BUILDING
Evening —Embassy Receptions by invitation for delegates from respective countries	

Wednesday, September 10

8 00 a m —Registration	DAIICHI BUILDING
9 00 a m —Scientific Sessions	DAIICHI BUILDING
2 00 p m —Scientific Sessions	DAIICHI BUILDING
8 00 p m —Congress Banquet	TOKYO KAIKAN

Thursday, September 11

8 00 a m —Registration	DAIICHI BUILDING
9 00 a m —Scientific Sessions	DAIICHI BUILDING
12 00 noon—Luncheon Meeting, Closing Executive Session, Regents and Governors	TOKYO KAIKAN
2 00 p m —Fireside Conferences	TOKYO KAIKAN
6 00 p m —Reception by Mr Seiichiro Yasui, Governor of Tokyo, at Chinzanso	

September 8-11

Motion Picture Sessions	DAIICHI BUILDING
Exhibits—Technical and Scientific	RED CROSS BUILDING

Ladies Activities
Fifth International Congress

Sunday, September 7

8 30 p m —Inaugural Ceremony and Convocation — YOMIURI HALL

Monday, September 8

10 00 a m —Tour of Tokyo
2 00 p m —Tour of Tokyo
6 00 p m —Reception by Hon Nobusuke Kishi, Prime Minister, at his official residence

Tuesday, September 9

10 00 a m —Kimono Fashion Show — TAKASHIMAYA DEPARTMENT STORE
2 00 p m —Flower Arrangement Demonstration — SOGETSU KAIKAN

Wednesday, September 10

9 00 a m —4 30 p m —Bus Tour to Kamakura and Enoshima (including lunch)
8 00 p m —Congress Banquet — TOKYO KAIKAN

Thursday, September 11

10 00 a m —Fashion Show — MITSUKOSHI DEPARTMENT STORE
2 00 p m —Tea Ceremony — CHINZANSO
6 00 p m —Reception by Mr Seiichiro Yasui, Governor of Tokyo, at Chinzanso

24TH ANNUAL MEETING

The 24th Annual Meeting of the American College of Chest Physicians was held at the Fairmont Hotel, San Francisco, June 18-22, the meeting was very successful with a registration of more than 1400 physicians and guests representing 46 of the States and a dozen other countries and territories Twenty-five technical exhibits, the maximum number that could be accommodated, were on display throughout the meeting

Fellowship Certificates were awarded to 160 physicians at the Annual Convocation of the College held on Saturday, June 21 Dr Donald R McKay, Buffalo, New York, incoming President of the College, addressed the Convocation assembly

The Convocation was followed by the Annual Presidents' Banquet which was attended by 495 physicians and members of their families A cocktail party, sponsored by the Panray Corporation of New York City, preceded the banquet Dr Burgess L Gordon, Albuquerque, New Mexico, President of the College, presided at the banquet and introduced the officials and special guests

Dr Walter B Brown, Livermore, California, Chairman of the Committee on Prize Essay Awards, introduced the first and second prize winners of the 1958 Essay Contest of the College First prize winner was Eugene Friedberg of the University of Buffalo, Buffalo, New York, who was presented with a certificate and a cash award in the amount of $500 00 for his essay "Murmur Production in Aortic Stenosis An Analysis Using a Hydraulic Model" Ronald J O'Reilly of the University of California at Los Angeles, received the second prize certificate and a cash award of $300 00 for his essay entitled "Clinical Recognition of Carbon Dioxide Intoxication" The third prize winner was Alan S Deutsch of the New York University College of Medicine, New York City, who was unable to be present Mr Deutsch received his certificate and award of $200 00 at a special presentation ceremony in New York arranged by Dr Coleman B Rabin, Governor of the College for New York State The com-

mittee awarded Honorable Mention and a prize of $50.00 to Miss June Hagen of the University of Cape Town Medical School, Cape Town, South Africa, for her excellent essay "Cryptococcosis of the Lung." The award was presented to Miss Hagen by Dr. David P. Marais, Regent of the College for South Africa, at a special meeting.

Presentation of the 1958 College Medal was made to Dr. J. Winthrop Peabody, Sr., Washington, D. C., by Dr. Gordon, for meritorious achievement in the specialty of diseases of the chest, particularly in the field of postgraduate medical education. Dr. Peabody has served as Chairman of the Council on Postgraduate Medical Education of the College since its inception in 1946. His photograph and biography appeared in the July issue of *Diseases of the Chest*.

The Immediate Past President of the College, Dr. Herman J. Moersch of the Mayo Clinic, Rochester, Minnesota, presented the Presidential Scroll to Dr. Gordon and the College Past-President's Pin to Mrs. Gordon.

Announcement was made of the approaching Fifth International Congress on Diseases of the Chest, to be held in Tokyo, Japan, September 7-11, under the sponsorship of the Council on International Affairs of the College. Through the kindness of Japan Air Lines, favors were distributed to the guests by two lovely girls wearing Japanese kimonos.

A Homecoming Meeting to be held in Albuquerque, New Mexico in October, 1959, in celebration of the 25th anniversary of the first College meeting, was announced at the banquet. A number of members from Albuquerque and their wives, dressed in typical Western style, distributed favors by courtesy of the Albuquerque Chamber of Commerce.

The evening closed with a dance sponsored by the California Chapter of the College.

Administrative Meetings

The annual meetings of the Executive Council, Board of Regents and Board of Governors were held in San Francisco where reports from the various councils and committees were received, and matters of policy discussed. The proceedings of these meetings and reports of councils and committees will be published in subsequent issues of the College journal.

On Saturday morning, June 21, the Open Administrative Session was held and reports were presented by the Treasurer, the Historian, the Executive Director and the Committee on Nominations. The following officers, Regents and Governors were elected.

Officers

President	Donald R. McKay, Buffalo, New York
President-Elect	Seymour M. Farber, San Francisco, California
1st Vice President	M. Jay Flippe, Miami, Florida
2nd Vice-President	Hollis E. Johnson, Nashville, Tennessee
Treasurer	Charles K. Petter, Waukegan, Illinois
Asst. Treasurer	Albert H. Andrews, Chicago, Illinois
Chairman, Board of Regents	John F. Briggs, St. Paul, Minnesota

Regents

District No. 2	Edgar Mayer, New York, N. Y.
District No. 4	Dean B. Cole, Richmond, Virginia
District No. 6	Howard S. Van Ordstrand, Cleveland, Ohio
District No. 9	David H. Waterman, Knoxville, Tennessee
District No. 10	Arthur M. Olsen, Rochester, Minnesota
District No. 14	Edward H. Morgan, Seattle, Washington
District No. 17	Thomas G. Heaton, Toronto, Canada
Historian	Carl C. Aven, Atlanta, Georgia

Governors

Delaware	Gerald A Beatty, Wilmington
Indiana	Jerome V Pace, Rockville
Iowa	William B Bean, Iowa City
Kentucky	John S Harter, Louisville
Massachusetts	Norman J Wilson, Boston
Montana	Lloyd M Taylor, Great Falls
Nebraska	Max Fleishman, Omaha
Nevada	Robert C Locke, Reno
New Hampshire	Francis J Kasheta, Glencliff
New Mexico	Joseph E J Harris, Albuquerque
Ohio	Ray W Kissane, Columbus
Oklahoma	Donald W McCauley, Okmulgee
Oregon	William S Conklin, Portland
Rhode Island	Frank A Merlino, Providence
South Carolina	J Gordon Seastrunk, Columbia
South Dakota	Robert C McCroskey, Rapid City
Tennessee	Duane Carr, Memphis
Wisconsin	Mischa J Lustok, Milwaukee

Announcement was also made that the Interim Session of the College would be held at the Mayo Clinic, Rochester, Minnesota on November 29 and 30, 1958 An outstanding scientific program, including formal papers, panel discussions, round table luncheons and fireside conferences, is now being organized by the program committee for the meeting Tours of the Clinic and an interesting display of scientific and technical exhibits will also be included The Board of Governors will hold its semi-annual meeting in Rochester on Saturday, November 28, and examinations for Fellowship, as well as meetings of various councils and committees will be held on that day

On Monday, December 1, the Board of Regents will hold its semi-annual meeting at the Radisson Hotel, Minneapolis A dinner and evening scientific session is also planned The Clinical Meeting of the American Medical Association will be held in Minneapolis, December 2 through 5, 1958

It was announced that the 25th Annual Meeting, Silver Anniversary, of the American College of Chest Physicians, would be held in Atlantic City, New Jersey, June 3-7, 1959 A number of special functions are being planned to celebrate the Silver Anniversary Meeting of the College

Ladies Activities

The ladies attending the 24th Annual Meeting of the College enjoyed a delightful program of activities arranged for them by Mrs Seymour M Farber and the members of her committee On Thursday, June 19, the ladies were taken to the Alta Mira Hotel in Sausalito for lunch, and from there to Jackson Square, one of the oldest sections of San Francisco, where they were taken on a tour of the Interior Decorator Display Shops A dinner party was arranged for the ladies at the Yamato Sukiyaki House on Friday evening, June 20, while their husbands attended the fireside conferences of the College Following the Japanese style dinner, a Japanese Fashion Show was presented for the ladies On Saturday evening, June 21, the ladies attended the Annual Convocation, cocktail party and Presidents' Banquet of the College held at the Fairmont Hotel Mrs Farber, Chairman, and Mrs Roger Wilson, Co-Chairman of the Ladies Committee, as well as the other members of the committee, are commended for the enjoyable program they prepared for the ladies and for the splendid manner in which the activities were handled

SCIENTIFIC PROGRAM COMMITTEE REQUESTS ABSTRACTS FOR SILVER ANNIVERSARY MEETING

The 25th Annual Meeting of the College will be held in Atlantic City, New Jersey, June 3-7, 1959 Special plans for the scientific program to be presented at the Silver Anniversary Meeting are now under way Physicians who wish to present papers are urged to submit a 200-word abstract to the appropriate committee chairman at the earliest possible date for consideration Please forward abstracts to one of the following co-chairmen

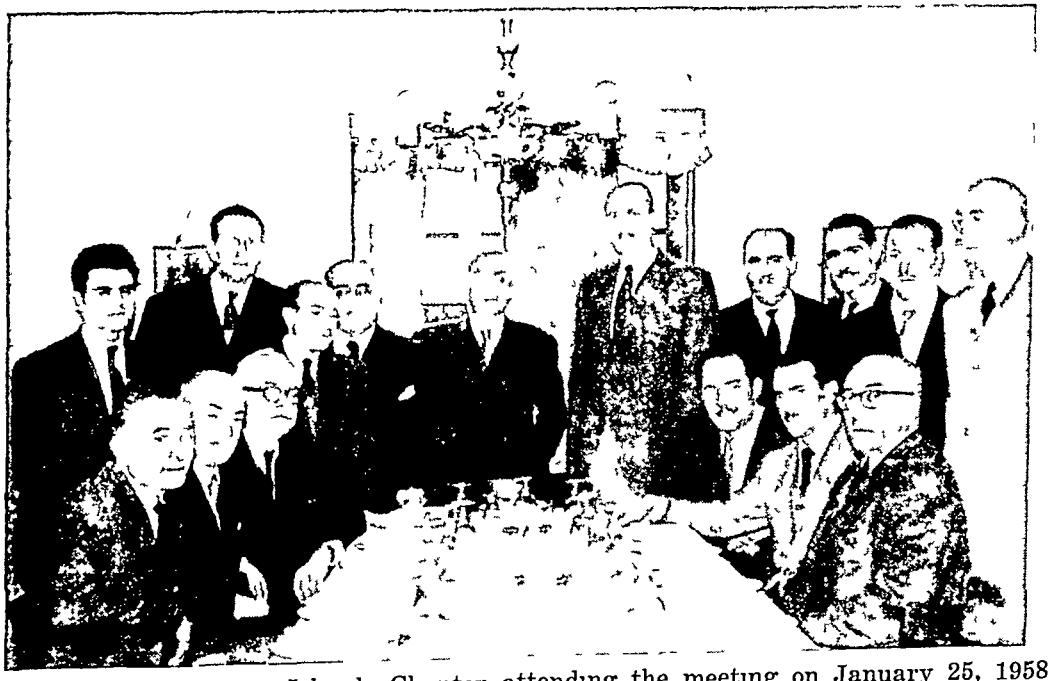
Dr Arthur M Master, 125 East 72nd Street, New York City
Chairman, Section on Cardiovascular Diseases
Dr Coleman B Rabin, 110 East End Avenue, New York City
Chairman, Section on Pulmonary Diseases

The Committee on Motion Pictures of the College will be interested to learn of new films on diseases of the chest for possible presentation at the 25th Annual Meeting in Atlantic City All pertinent information concerning films should be forwarded to Dr Paul H Holinger, chairman of the committee, 112 East Chestnut Street, Chicago 11, Illinois The committee will be pleased to review films for official approval and inclusion in the Approved Film List of the American College of Chest Physicians

College Chapter News

CANARY ISLANDS CHAPTER

The Canary Islands Chapter met at Santa Cruz de Tenerife on January 25, at which time the executive council discussed future chapter activities Following the business meeting, a panel discussion on the subject "Preparation of the Patient for Thoracic Surgery" was held Dr Tomas Cervia, Governor of the College for the Canary Islands, presided at the scientific session The next meeting of the chapter was held in Las Palmas on May 10 at which a program dealing with "Present Day Treatment of Pulmonary Tuberculosis" was presented



Member of the Canary Islands Chapter attending the meeting on January 25, 1958 *Seated, left to right* C R Gavilanes, President of the Chapter, Jose Pérez Perez, Chapter Treasurer, José Gerardo Martin Herrera, D Ponce Arencibia, Miguel Cuesta Palomero and Jose Estrada *Standing, left to right* Enrique Gonzalez, Secretary of the Chapter, Agustin Bosch Millares, V Navarro Marco, Jose Dominguez, Tomas Cervia, Governor, Augusto Mendez de Lugo, J M del Arco Montesinos, Vice-President of the Chapter, M Garcia Gonzalez, Francisco Perez Perez, and Ramon Luelmo

ANDALUSIAN CHAPTER

Members of the College in Spain met recently to form the Andalusian Chapter The following officers were elected

President	Norberto Gonzales de la Vega, Granada
Vice-President	Salvador Almansa de Cara, Malaga
Secretary	Antonio Azpitarte Rubio, Granada
Treasurer	Carlos Gomez-Moreno, Granada

PANAMANIAN CHAPTER

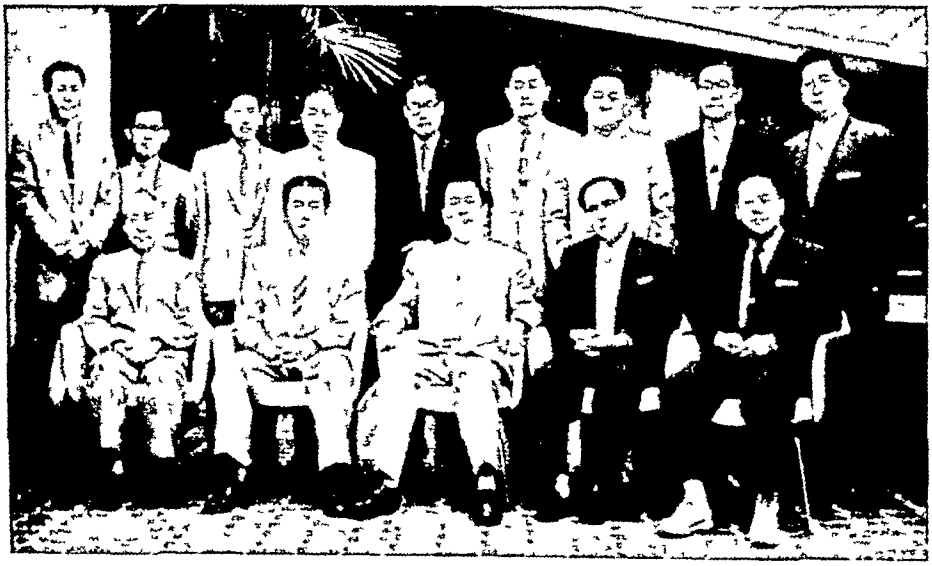
The Panamanian Chapter of the College met on May 3, 1958 in David, Republic of Panama in conjunction with the Panamanian Association of Phthisiologists Dr Maximo Carrizo Villareal, Regent of the College, presented a paper on "Tuberculin Prevention in 778 Children in Colon"

KOREAN CHAPTER ORGANIZED

The Korean Chapter of the College was officially organized at an inaugural meeting held in the Dynasty Room of the Bando Hotel, Seoul, on June 16, 1958 The meeting was called to order by Dr Eung Soo Han, Governor for the College for Korea, who gave a brief review of the activities of the College in that country The following officers were elected

President	Chai Kyu Hans Lee, Seoul
1st Vice-President	Kyung Sik Kim, Seoul
2nd Vice-President	Chan Sae Lee, Pusan
Secretary-Treasurer	Eung Soo Han, Seoul
Assistant Secretary-Treasurer	Pyoung Ki Kim, Masan
Chairman, Program Committee	Pill Whoon Hong, Seoul

Dr Eung Soo Han was appointed official chapter representative to attend the International Congress in Tokyo



Members of the College attending inaugural meeting of the Korean Chapter (left to right) First row Drs Sock H Shin, Kyung Shik Kim, Chai Kyu H Lee, Chan Se Lee, and Eung Soo Han, Second row Pill Whoon Hong, Pyoung Ki Kim, Y C Park, Byung Suh Yu, Kiho Kim, Hi Myung Park, Lee Gap Park, N K Kim, and K H Yoo

NEW MEXICO CHAPTER FOUNDED

On May 16, following the first scientific session presented by the New Mexico Chapter of the College, Dr Burgess L Gordon, Immediate Past-President of the American College of Chest Physicians, installed the New Mexico Chapter as the 73rd chapter Dr Carl H Gellenthien, Valmora, was elected President, Dr J E J Harris, Albuquerque, President-Elect, Dr Joseph Gordon, Albuquerque, Vice-President, and Dr Roy F Goddard, Albuquerque, Secretary-Treasurer

At this session, charter members of the College, Drs Carl H Gellenthien and J E J Harris, were honored at a banquet

The New Mexico Chapter will be host to members of the College for the 25th Anniversary Homecoming Meeting to be held in Albuquerque in the fall of 1959

Fellows of the College participating in the founding of the New Mexico Chapter (left to right) Drs Roy F Goddard, Albuquerque, R Drew Miller, Rochester, Minnesota, Edwin R Levine, Chicago, Burgess L Gordon, Albuquerque, Albert H Andrews, Chicago, and Mr Murray Kornfeld, Executive Director, Chicago

NEW CHAPTER OFFICERS

ALABAMA CHAPTER

President	Arthur A Calix, Decatur
Vice-President	Justus M Barnes, Birmingham
Secretary-Treasurer	William J Tally, Gadsden

CALIFORNIA CHAPTER

President	Elmer C Rigby, Los Angeles
Vice-President	Thomas B Wiper, San Francisco
Secretary-Treasurer	Samuel J Sills, Los Angeles

FLORIDA CHAPTER

President	George L Baum, Coral Gables
Vice-President	M Eugene Flipse, Miami
Secretary-Treasurer	Ivan C Schmidt, West Palm Beach

GEORGIA CHAPTER

President	James L Alexander, Jr , Savannah
Vice-President	M Bedford Davis, Jr , Atlanta
Secretary-Treasurer	Lawrence Lee, Jr , Savannah

KANSAS CHAPTER

President	Robert M Brookes, Topeka
Vice-President	John K Fulton, Wichita
Secretary-Treasurer	Roy A Lawson, Chanute

MICHIGAN CHAPTER

President	Stephen M Gelenger, Flint
Vice-President	Nathan Levitt, Detroit
Secretary-Treasurer	James T Cheng, Pontiac

MISSOURI CHAPTER

President	David M Skilling, Jr , St Louis
Vice-President	Ellis S Lipsitz, St Louis
Secretary-Treasurer	David Nafe Kerr, St Louis (re-elected)

OHIO CHAPTER

President	Harvey Mendelsohn, Cleveland
Vice-President	George Kress, Columbus
Secretary-Treasurer	F G Kravec, Youngstown (re-elected)

OKLAHOMA CHAPTER

President	Robert M Shepard, Jr , Tulsa
Vice-President	Philip M McNeill Oklahoma City
Secretary-Treasurer	George L Winn, Oklahoma City

PERU CHAPTER

President	Mario Pastor B , Lima
Vice President	Marino Molina, Lima
Secretary	Alejandro A Castro, Lima
Treasurer	Jose Maria Almandos Velis, Lima

TEXAS CHAPTER

President	J Otis Armstrong, Dallas
1st Vice-President	Lawrence M Shefts, San Antonio
2nd Vice-President	Hiram M Anderson, San Angelo
Secretary-Treasurer	Carlos J Quintanilla, Harlingen

URUGUAY CHAPTER

President	Juan E Alejandro Victorica, Montevideo
Secretary-Treasurer	Rene Racine, Montevideo (re-elected)

WISCONSIN CHAPTER

President	Ross C Kory, Wood
Vice-President	Leon Hirsh, Milwaukee
Secretary-Treasurer	Raymond R Watson, Milwaukee

NEWS NOTES

The first annual Marcy Lecture, honoring **Dr C Howard Marcy,** Pittsburgh, Pennsylvania, was delivered by **Dr Esmond R Long,** former director of medical research for the National Tuberculosis Association Dr Marcy, a Fellow of the College, has served as the medical director of the Tuberculosis League of Pittsburgh for twenty-nine years

Dr William C Voorsanger, San Francisco, was honored by the San Francisco Tuberculosis Association at its Fiftieth Anniversary Luncheon on April 1 Dr Voorsanger received a sterling silver tray as a tribute to his many years of service as founder, director and secretary of the Association

Prof Dr Aloysio de Paula, President of the Rio de Janeiro Chapter of the College and Professor of Phthisiology, University of the Federal District Medi-

cal School, Rio de Janeiro, was recently appointed Professor of Phthisiology at the State of Rio University Medical School This appointment was made after Dr de Paula's thesis, "Thoracoplasty and Resection in the Treatment of Pulmonary Tuberculosis" was judged the best paper in the competition for the position Professor de Paula, one of the pioneers in Abreugraphy, is President of the Brazilian Tuberculosis Society and Director of the Tuberculosis Service of the Rio de Janeiro General Policlinic

Prof. Dr **Manoel de Abreu**, Rio de Janeiro, Brazil, Regent of the College for Southern Brazil, was recently made a member of the Order of Medical Merit and received the Great Cross of the Order in honor of his outstanding work in the field of tuberculosis and for his discovery of the method of roentgenphotography now called "Abreugraphy" His birthday, January 4, has been set aside by official government decree as "Abreugraphy Day" The Brazilian Society of Abreugraphy was organized on November 30, 1957 in the State of Rio, in which the movement to honor Prof Abreu originated

Dr *Sol Katz, Washington, D C, received the first* Edward Y Davidson Award presented by the Medical Society of the District of Columbia for the best scientific paper published in the *Medical Annals of the District of Columbia* during 1957

Dr **Arthur E Strauss**, St Louis, Missouri, recently received the first distinguished achievement award made by the St Louis Heart Association

Dr **Fred M F Meixner**, Peoria, Illinois, was awarded the Alma B Fringer Memorial Award of the Illinois Tuberculosis Association for "truly outstanding service in the field of tuberculosis"

Dr **C Walton Lillehei**, Minneapolis, Minnesota, will receive the Oscar B Unter Memorial Award of the American Therapeutic Society during the society's 49th annual meeting in San Francisco on June 21

Dr **George R Herrmann**, Galveston, Texas, was recently elected Vice President of the Texas Academy of Internal Medicine

Colonel Najib Khan, Hyderabad, West Pakistan, has been elected President of the Medical and Veterinary Section of the Pakistan Science Conference

Dr **O Theron Clagett**, Rochester, Minnesota, was elected to honorary membership in the Irish College of Surgeons in Dublin on February 15 Dr Clagett delivered the Abraham Colles Lecture at the Charter Day meeting of the organization

Dr **William Likoff**, Philadelphia, Pennsylvania, participated in the recent Fifth Biennial Cardiovascular Seminar of the Heart Association of Greater Miami

The late Cardinal Stritch of Chicago conferred the Pontifical order, Knight of St Gregory, on Dr **John L Keeley** of Chicago

ANNOUNCEMENTS

A three-day international symposium on the status of tuberculosis as a public danger will be held in Philadelphia, November 20-22, at the Bellevue-Stratford Hotel, under the auspices of the Deborah Tuberculosis Sanatorium and Hospital of Browns Mills, New Jersey Subjects to be discussed are epidemiology, mortality and morbidity changes, case finding programs, bacteriological aspects, prophylaxis including the status of BCG and isoniazid prophylaxis, surgical aspects of tuberculosis treatment, chemotherapy of tuberculosis, drug resistance, the open negative case and its various implications of public health management Members of the planning committee are Drs Charles P Bailey, Nathan Ralph, Henry Nichols, Joseph M Fruchter and Paul K Bornstein

---

The Panray Corp, full line drug manufacturer in the human and veterinary fields, has opened a new industrial plant in Englewood, New Jersey

DISEASES of the CHEST

VOLUME XXXIV SEPTEMBER, 1958 NUMBER 3

Speculations on the Future Treatment and Control of Tuberculosis*

H CORWIN HINSHAW, M D , F C C P

San Francisco, California

Speculations about the future appeal to us all Someone has said that he was mostly interested in the future because he expected to spend the rest of his life there

Trends have become established in the fields of tuberculosis control and treatment which, if they continue in their present direction, may well affect the practice of medicine in a radical manner Is it possible that home treatment will supplant sanatorium treatment? Or, on the other hand, will the present trend to socialization of tuberculosis medicine continue, with less and less of private practice? Is the time near when the 100,000 beds now occupied by patients with tuberculosis can be used for other purposes? Can the taxpayers be relieved of the enormous cost of the Veterans Administration Tuberculosis program? Is it possible that the present Veterans monetary benefits for disability from tuberculosis can be abolished, assuming that no true disability exists following successful modern treatment?

Most importantly, are we as physicians doing all that we could do to direct the stream of events in this changing field? If we can agree on what is right and what is best for our patients and the public we should bend all efforts to see any necessary reforms enacted to bring about what is best

Most of us serve as doctors—physicians is a better word—and we serve individuals, rather than the mass of men While we are interested in local and national statistics, it is in a rather detached way, for what we do as individuals carries little weight in the broad sense We serve as *personal* physicians—I like that word, use it often—we are *personal* physicians to rather small numbers of people We are responsible for their health and welfare, but we share their other problems, their triumphs as well as their problems We seek, above all, to protect them from the dangers of disease, especially the unseen health hazards from which they cannot protect themselves Let us promote the idea that each man, woman and child should choose a personal physician and refer to him all health problems

*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

**Clinical Professor of Medicine, Stanford University School of Medicine

Copyright 1958 by the American College of Chest Physicians

The personal physician, not the public health clinic, is the one to whom the patient of the future may look for protection against perils of thoracic disease I mention thoracic disease, not alone because I am talking to this group, but because such conditions as degenerative heart disease, bronchogenic carcinoma and even tuberculosis are profoundly important to those who have chosen you as their personal physician Perhaps these diseases are preventable—you might want to argue that point—but they are detectable, especially the pulmonary diseases, by the rather simple means of chest x-ray I have included tuberculosis in the list because its curability is nearly 100 per cent in those persons who have annual chest x-ray films and are well advised about the findings I should stress bronchogenic carcinoma because of its mounting prevalence and the urgent need for its recognition *before* it produces symptoms Of the visceral cancers it is one of the most curable when treated during the earliest stage at which it can be detected—few cancers of man can be detected so early, by the personal physician

Minifilms vs Megafilms

Case finding, another word for diagnosis, is the obvious "sine qua non" in all tuberculosis endeavour, whether private practice or public health The minifilm mass survey technique has now undergone thorough trial and demonstration It has served as a great educational method, for doctors as well as the public It is my opinion that the future use of this technique is predictable It will not be used for periodic mass surveys of the general public in the United States, the task is too great and the yield is now too small for the true cost of such undertakings On the other hand, special population groups should be surveyed by this or another method I refer to groups with a high incidence of tuberculosis, food handlers, prisoners and inmates of charity hospitals and domiciliary institutions School teachers, "baby sitters" and others who associate closely with children constitute a special group

There is no virtue in minifilms, as such Even the factor of economy has been exaggerated greatly Economy is partly the result of hasty diagnosis by "cheap help" or donated services It should take more time, not less time, and more skill, to study a minifilm accurately and since time is a most expensive ingredient in total true cost the conventional 14 × 17 film may be the cheapest Cost of equipment and its depreciation may exceed the cost of film when the number of patients is small

We cannot pass the subject of minifilms without mention of radiation exposure There has been much speculation and no little hysteria about exposure hazards in radiology Chest x-ray films are less hazardous than many radiologic examinations because (1) little radiation is necessary for penetration of the air-containing thorax (unlike the abdomen), (2) there need be no direct radiation of the reproductive organs and scatter radiation is extremely slight (a luminous dial wrist watch provides as much radiation in one week as a chest x-ray film) Nevertheless we must call your attention to the fact that one minifilm involves as much radiation exposure as 10 to 25 14 × 17" films Whenever the factor of exposure

is considered—as in children—preference should be for the 14 × 17″ chest film One complete "G I series" may involve as much gonadal exposure as scores or hundreds of chest x-ray films

If the fears of the alarmists should be substantiated, radiologic examinations of the future may be done by means of amplified images, a technique resembling television which could reduce radiation to a negligible amount There is not the slightest reason to fear the annual or semi-annual conventional chest x-ray film, in my opinion If minifilms are to be used it might be desirable to use only the new mirror cameras with such great light gathering capacity as to reduce exposure and scatter considerably Each of us should determine if our patients are receiving needless radiation because of failure to provide limiting cones or similar screens for the gonads

State Medicine vs Private Medicine

It has become tradition in many communities that tuberculosis problems will be cared for by public agencies This is based upon the supposition that private care is too expensive or not good enough and the fact that this is a contagious disease The time may be approaching when these suppositions can be questioned and these facts modified

Speaking of quality of medical care, I doubt if any community now lacks private physicians who are thoroughly trained in the management of pulmonary diseases Good radiologic and laboratory services are available universally throughout this country These conditions did not exist 20-30 years ago when many of the present regulations were devised

The cost of treating tuberculosis has diminished and may be even further reduced Prolonged and stringent bed rest is no longer necessary Often an "attack" of tuberculosis involves less expense and less disability than a heart attack and certainly tuberculosis is much the less common of the two

I have a concrete proposal for the insurance companies and welfare funds which now exclude tuberculosis coverage When writing a policy for sickness expense insurance (don't say health insurance) offer to cover tuberculosis treatment for anyone who will submit a negative chest x-ray film and who has annual films thereafter I don't believe that the claims will be appreciable

Tuberculosis is a contagious disease It is essential that those who might disseminate the infection be treated until they are safe associates The public must supply this service if it is not provided for otherwise, not only for tuberculosis but also for the many other dangerous contagious diseases Formerly tuberculosis was communicable for a long period, but this situation has changed A great majority of patients, certainly more than 90 per cent of those who accept modern therapy and even a greater percentage of those who have had annual negative chest x-ray films, will cease to disseminate tubercle bacilli within several weeks after treatment is started The time is approaching—perhaps it is here—when tuberculosis need not be considered as a problem of state medicine, without

regard to the economic status of the patient, because of its public health aspects

If patients are to pay for care of tuberculosis through prepaid insurance—and I firmly believe that they should and can do so—our public hospitals should be able to recover costs of treating such patients Often this is now the case but in the future this source of revenue may largely supplant the contributions of the taxpayer, a welcome change for taxpayers and politicians alike

In this day of reduced tuberculosis bed occupancy it is interesting to see the development of a real sense of *competition for the patient* For example, the veteran may choose between the county hospital, a private hospital (through insurance benefits) or a Veterans Administration Hospital Each of these is bidding for his patronage and attempting to deserve it by improvements in service Here, as never before, the spirit of competition may serve a noble purpose

Speaking of costs, the cost of a good individual sickness expense insurance policy which covers nearly all diseases is about the same as the cost of one package of cigarettes daily The cost may be less than this for the more sensible deductible types of policies Anyone who can afford to smoke can afford to buy such insurance Tell that to your patients—but frequently. Another comparison, the annual cost of all inclusive medical care throughout a lifetime is less than the cost of keeping an automobile in repair An ordinary illness costs less than a minor automobile repair bill or a smashed fender from a minor accident A serious illness costs less than trading in the serviceable old car on a new model

Dare we predict that patients can be taught the relative values and relative costs of such things as medical care and automobile care? If not is it reasonable to propose that the government should buy us new tires and clean our spark plugs rather than supply us with some health services which we may consider less important? These problems of medical economics should be the task of doctors, not politicians

Treatment of Recently Converted Tuberculin Reactors vs Vaccination

This is logical and may well become standard practice My appeal will be for some truly adequate study to determine the needs and techniques for therapy If a simple treatment, such as isoniazid alone, is adequate the procedure will become very popular I, among many of you, have serious doubt about the adequacy of isoniazid alone Simply because we are treating an invisible infection and a symptomless one does not necessarily imply that it will be overcome more readily Actually we are treating this patient for all time to come We are aiming at eradicative therapy, if at all possible, and this is truly a big task for isoniazid alone

Much of our reasoning in tuberculosis problems has been on a mass population basis I expect to see more personal consideration of such problems in the future The pediatricians are doing it now *Many children* receive annual tuberculin tests and some who convert will be treated As soon as these people cease to be children the risk does not cease, yet it is forgotten I believe that the personal physician of the immediate

future will carry out an annual birthday health appraisal examination, including a tuberculin test Prophylactic treatment at the time of conversion is a logical substitute for BCG vaccination and on the whole more practical in the U S A

If non-living antigenic material is ever extracted from the tubercle bacillus such preventive treatment may become popular in this nation

There is no longer any question about the relative efficacy of vaccination in tuberculosis There also is no longer any doubt in the minds of many but that immunization is far from the answer to the problems of tb control

BCG is indicated in those areas of the world where a majority of persons become sensitized to tuberculin spontaneously This simple formula seems to be a reasonable reply to the ever recurrent question of where to recommend mass immunization There is still hope that some non-living immunizing agent may be developed Lacking this we should direct our attention to the vole bacillus or similar vaccine which does not consist of tubercle bacilli, not so much because it is better or safer but just to quiet any unanswerable arguments against the inoculation of tubercle bacilli into defenseless babies by big brutes of men

According to newspaper reports mass vaccination on a compulsory basis was instituted in the Soviet Union in 1937, yet the death rate from tuberculosis nearly 20 years later is said to be about 40 per 100,000 One week from today I expect to arrive in Moscow to attend the Sixth All-Union Congress on Tuberculosis and am anticipating this opportunity of learning at first hand the opinions of those physicians who have observed compulsory vaccination during these 20 years

The Tuberculosis Associations and the Medical Profession

These have been the most successful and the most effective organizations of their kind in history I am certain that we are infinitely more advanced in the program for the eradication of tuberculosis because of the National Tuberculosis Association and its affiliate local and state organizations I believe that the medical profession should support and guide these groups which are primarily Health Educational and Propaganda groups They need and they want medical guidance and although they have good medical guidance at the national level there is much need for greater participation by doctors at the community level Any decline in the effectiveness of the tuberculosis association would be a real blow to every man in this room Your effectiveness as a doctor in the field of chest diseases would diminish

The Veterans Administration

We have witnessed the development of a great medical organization in a little more than 10 years, an organization within an organization—the Tuberculosis Service of the Department of Medicine and Surgery of the Veterans Administration This organization has had much to do with improving the way you and I practice medicine Right now it is facing some new problems related to the diminished needs for its services to

patients, simply because it has done its task so well I would be glad to give the Veterans Administration some unsolicited advice here Fewer patients means fewer doctors, so here is a chance to improve the quality of your staff by reducing its quantity Don't cut pay or reduce opportunities as you contract, reward your best men as you release the others There will always be a *good* job for the *devoted* doctor in the Veterans Administration By all means continue your educational and research activities to draw and hold the scholarly type of doctor By all means retain and strengthen your relationships with the medical schools—the mutual advantages of this relationship cannot be overestimated So, I predict, a smaller, more select, and no less effective elite corps of Veterans Administration physicians who will continue as leaders in this field, academically as well as in clinical practice

I predict that expense to taxpayers can be reduced further by a realistic review of the disability benefits paid to veterans who have had tuberculosis Those who were disabled by service connected tuberculosis deserve more generous compensation Those who were not disabled deserve *none* Modern treatment frequently restores the patient with tuberculosis to full productive capacity

Tuberculosis and the Armed Forces

Tuberculin testing, now well established by the Navy, is ideally suited to the needs of the armed forces as a tool for detection of tuberculous infection This is particularly important because 90-95 per cent of recruits enter service with negative skin tests Their duties carry them occasionally to parts of the world where opportunity for infection is great Such infections should be service connected, even if only identified by a conversion of the tuberculin test Possibly they should be treated at this stage—perhaps the armed forces could determine for us, by means of a well designed study, if they need to be treated

Conclusions

You and I are interested in the future—we expect to spend the rest of our lives there We expect to see more of preventive medicine in private practice We expect to see more patients coming for annual birthday examinations which will include a chest x-ray film We expect that when tuberculosis is found the cost of care will be borne by sickness cost insurance which the patient has been paying for on a voluntary basis While care of the active disease may be in a hospital under the care of specialists, the patient will soon return to his home and his job and the care of his "personal physician" The annual examination of adults will include a tuberculin test, just as is now practiced by pediatricians Conversion to a positive test may or may not require treatment but it will alert the physician to the significance of any newly developed pulmonary disease Such management in the Armed Forces, as well as among civilians, will lead to new concepts of service connected tuberculosis Our present laws and regulations regarding compensation are due for drastic and realistic

revisions Already tuberculosis is losing its reputation as a killer and crippler in war and peace

The future is destined to be a pleasant place for spending the remainder of our lives—just as the past has been

SUMMARY

The personal physician should expect to serve ever more important functions in preventive medicine and public health

Minifilm surveys of the future are likely to be limited to special population groups who face unusual hazards of thoracic disease

Insurance against expenses of illness should cover such catastrophes as pulmonary tuberculosis Present day methods of treatment have reduced the cost of treatment and the prevalence of the disease has diminished sufficiently so that such insurance need not be expensive

Diminished bed occupancy of tuberculosis hospitals should permit the abandonment of less effective institutions and improvement of the surviving hospitals

The treatment of recently converted tuberculin reactors appears to be a logical and feasible substitute for BCG vaccination in many social groups in the U S A

Physicians in private practice should provide more direct personal support and encouragement to local and state tuberculosis associations

The Veterans Administration and the Armed Forces will continue to provide leadership in the field of tuberculosis and related problems

RESUMEN

Es de que el médico personal especialarse tenga siempre más importantes funciones en la medicina preventiva y en la salubridad pública

Las investigaciones por roentgenfotografía en el futuro, es posible que se limiten a grupos especiales de población que se enfrenten a peligros extraordinarios en relación a las afecciones torácicas

Los seguros contra gastos de enfermedad deben cubrir la tuberculosis pulmonar Los métodos actuales de tratamiento han reducido el costo del tratamiento y la prevalencia de la enfermedad ha disminuido suficientemente de manera que el seguro no debe ser costoso

La disminución del número de camas ocupadas debe permitir el abandonar las instituciones menos efectivas y mejorar los hospitales que restan

El tratamiento de los reactores que han virado recientemente parece ser un substituto lógico del BCG en muchos grupos sociales de los Estados Unidos

Los médicos en la práctica privada deben dar mayor apoyo directo y personal a las asociaciones antituberculosas locales

La Administración de Veteranos y las Fuerzas Armadas continuarán proporcionando siendo guías en tuberculosis y en los problemas que con ella se relacionan

RESUME

On devrait s'attendre a ce que les fonctions du médecin personnel soient de plus en plus importantes en médecine préventive et dans le domaine de la santé publique

Les examens radiophotographiques de l'avenir pourront se limiter à des groupes spéciaux de la population exposés de façon inhabituelle aux risques des affections thoraciques

L'assurance-maladie devrait couvrir les catastrophes telles que la tuberculose pulmonaire Les méthodes actuelles de traitement ont réduit les frais de traitement et la fréquence de la maladie a diminué suffisamment L'assurance pourrait en conséquence ne pas être d'un prix élevé

La diminution de l'occupation des lits dans les hôpitaux pour tuberculeux devrait permettre d'abandonner les établissements moins actifs et d'améliorer les autres

La traitement des individus ayant récemment viré leurs réactions tuberculiniques semble devoir remplacer la vaccination par le B C G Le procédé paraît logique et réalisable dans beaucoup de groupes sociaux aux Etats-Unis

Les médecins de clientèle privée devraient apporter une aide plus directe et un encouragement aux associations tuberculeuses locales et départementales

L'Administration des Vétérans et des Forces Armées continuera à prendre la tête de la lutte contre la tuberculose et des problèmes qui lui sont liés

ZUSAMMENFASSUNG

Vom einzelnen Arzt muss man erwarten, dass er immer wichtigere Aufgaben in der praventiven Medizin und dem offentlichen Gesundheitswesen dient

Kleinbild-Rontgenaktionen sind in Zukunft wahrscheinlich begrenzt auf spezielle Bevolkerungsgruppen, die ungewohnlichen Wagnissen hinsichtlich thorakaler Erkrankungen gegenuberstehen

Eine Versicherung fur die Unkosten bei Erkrankung sollte gegen solche Schicksalsschlage wie Lungentuberkulose schutzen Die Methoden der Behandlung von heute haben zu einer Verringerung der Kosten der Behandlung gefuhrt und die Krankheitshaufigkeit ist soweit zuruckgegangen, dass eine solche Versicherung nicht kostspielig zu sein braucht

Verminderte Bettenbelegung in Tuberkulose-Anstalten muss es ermoglichen, wenig rentable Einrichtungen aufzugeben und die ubrigen Anstalten zu verbessern

Die Behandlung von Fallen mit frisch positiv gewordener Tuberkulinreaktion scheint ein logischer und moglicher Ersatz fur die BCG-Impfung in vielen sozialen Gruppen in den USA zu sein Die Arzte in der freien Praxis sollten den orthchen und staatlichen Tuberkulose—Vereinigungen eine mehr direkte und personliche Unterstutzung und Anregung gewahren

Die Versehrtenverwaltung und die bewaffneten Streitkrafte werden darin fortfahren, fur die Leitung auf dem Gebiete der Tuberculose sowie mit ihr verwandter Gebiete zu sorgen

Emphysema and the Lungs of the Aged
A Clinical Study*

Preliminary Report

EDGAR MAYER, M D , F C C P , CHARLES BLAZSIK, M D , F C C P
and ISRAEL RAPPAPORT, M D , F C C P
New York, New York

Pulmonary emphysema has long remained an enigmatic disease Regarding its origins and nature, we are still much in the dark It is generally held to be a disease of advancing age This and its rising incidence, an increase parallel with the rising proportion of the aged population, naturally led to the assumption of a direct link with aging, and to an association with the aging process All of this has only added to the already existing confusion regarding this disease

In a recent publication we discussed current misconceptions about "senile emphysema" and drew the following conclusions

1 In the aged, emphysema clinically is not a prevalent disease

2 It is clinically no different in old people than in the younger age groups

3 The changes occurring with aging of the lungs and chest are now wrongly identified with emphysema

To test the validity of these conclusions we have been conducting a clinical study in a large geriatric institution We will here present and discuss the preliminary findings

Nature of the Study

This strictly clinical study is intended as an analysis of the prevalence and the distinguishing features of emphysema in the aged It is in progress at the Francis Scherviei Home and Hospital for the Aged Of 420 men and women residents, the majority (88 per cent) are admitted to the home in so-called normal health for their age A minority (12 per cent) are admitted as patients to the hospital division Their age and sex distribution are shown in the following table which also includes our findings

In each case we included a detailed clinical history and complete physical examination, particularly emphasizing the study of the chest Periodic x-ray films of the chest were available and it was possible to review serial films often extending over 8 to 10 preceding years Supplementary clinical laboratory data were obtained when required and in selected cases vital capacity and timed vital capacity studies were included

Findings and criteria As the table indicates, we found 18 cases of clinical pulmonary emphysema These could be readily distinguished

* The Seventh Howard Lilienthal Lecture presented at the annual meeting, New York State Chapter, American College of Chest Physicians, New York City, May 27, 1957

from changes in the lungs and chest attributable to aging, designated here as "senile lung"

The diagnosis of emphysema was made on the basis of accepted clinical criteria familiar to all These were the usual symptoms and signs of bronchial obstruction Clinically manifest emphysema in these aged men and women appeared in no way different from that of younger people It is also noteworthy that of these 18 cases, 15 were men, indicating a marked sex predilection *Emphysema is predominantly a disease of men regardless of age*

In contrast to this, women showed a marked tendency toward changes in the lungs and chest due to aging, *namely "senile lung"* We do not consider that the features of "senile lungs," to be described below, constitute a disease entity Clinically the aged women and men showing these features have practically no symptom or sign of pulmonary disease Their lungs are quite efficient for their age, especially within the increasingly restricted range of activity which naturally goes with progressive aging

The diagnosis of "senile lung" was made only in the absence of symptoms and signs pertaining to obstructed breathing and hyperinflated lungs and when physical signs that we now consider normal for old men and women were present These are

On inspection, the upper part of the chest may or may not appear distended and the lower halves may appear contracted, depending upon the degree of stooped shoulders The chest as a whole, however, is *not* overdistended

On percussion hyperresonance of variable degree may be found It appears to be restricted to the upper anterior part of the chest

Auscultation The outstanding clinical feature appears to us to be the type of breathing It is quiet, faint, shallow, seemingly effortless, and of a slightly accelerated rate Very few if any rhonchi are heard This contrasts rather vividly with the slower labored and more noisy breathing of the emphysematous aged patient On inducing a cough or on exercise, in the case of senile lungs, one can usually bring about short bursts of sharp and almost juvenile breath sounds We interpreted this as signifying that basically lung function was adequate On the other hand,

TABLE I

AGE AND SEX DISTRIBUTION OF SENILE LUNGS AND PULMONARY EMPHYSEMA AMONG 420 RESIDENTS OF THE OLD AGE HOME AND HOSPITAL OF FRANCES SCHERVIER, RIVERDALE, N Y—1956

Age group	65-69		70-74		75-79		90-84		85-89		90-94		95-99		100		Total	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total	21	45	32	53	39	93	21	44	19	23	7	7	6	14	—	1	140	280
Senile Lung	—	1	1	4	3	17	3	15	8	17	3	6	3	11	—	1	31	69
Emphysema	—	—	2	2	8	1	3	—	2	—	—	—	—	—	—	—	15	3

in emphysema of the aged, exercise further impairs breathing and exaggerates the previous signs and symptoms of bronchial obstruction

On fluoroscopy with a maximal effort of breathing, especially with cough, one can elicit fair movement of chest and diaphragms This we repeatedly confirmed even in those aged who at first seemed to have an almost fixed chest

The x-ray pattern which we have come to associate with the "senile lung" seemed significant In a review of nearly two thousand x-ray films of these aged men and women we identified certain suggestive features A spongy or lacy pattern of the lung fields associated with increased peripheral lung markings and an enhanced contrast of pulmonary markings seems to stand out The volume of the lung fields appears diminished, due particularly to narrowing of the chest cage in its lower third where the ribs appear to be more closely approximated By comparison, the heart often appears enlarged The upper halves of the chest are often vaulted due to stooped posture It should be emphasized, however, that the senile lung changes were rarely recognizable roentgenographically under the age of 80

Although we consider these findings as preliminary in nature we think they warrant tentatively the following conclusions

1 As a clinical entity chronic pulmonary emphysema in the aged occurs far less frequently than is generally assumed

2 Its clinical features in the aged (physical, fluoroscopic and x-ray signs) are indistinguishable from emphysema in the young

3 In a considerable proportion of aged women and men, changes are discernible in the chest and lungs which in themselves do not give rise to clinical symptoms and are not associated with the clinical features of emphysema These are best designated as "senile lungs" (or lungs of the aged)

Our findings therefore essentially confirm the concepts we discussed in a recent publication [1]

Discussion

A number of points pertaining to our observations deserve special consideration The preliminary data presented above are naturally limited to changes discernible by our methods of study, which are rather inadequate By the criteria mentioned we were able to reveal the presence of senile lung changes in only a minority of aged persons examined There is a need, of course, of correlating clinical, functional and morphological studies in an adequate number of cases, for which we so far have had too few opportunities We hope to be able in the near future to present a complementary study along these lines

Regarding the morphologic features of emphysema and "senile lungs" it should be noted that there is a considerable amount of information already available in recent literature It is rather gratifying to us that our preliminary findings reconcile the seemingly conflicting conclusions (recently reported by Monroe in America and Howell in England) which were drawn from extensive studies of large numbers of autopsies on

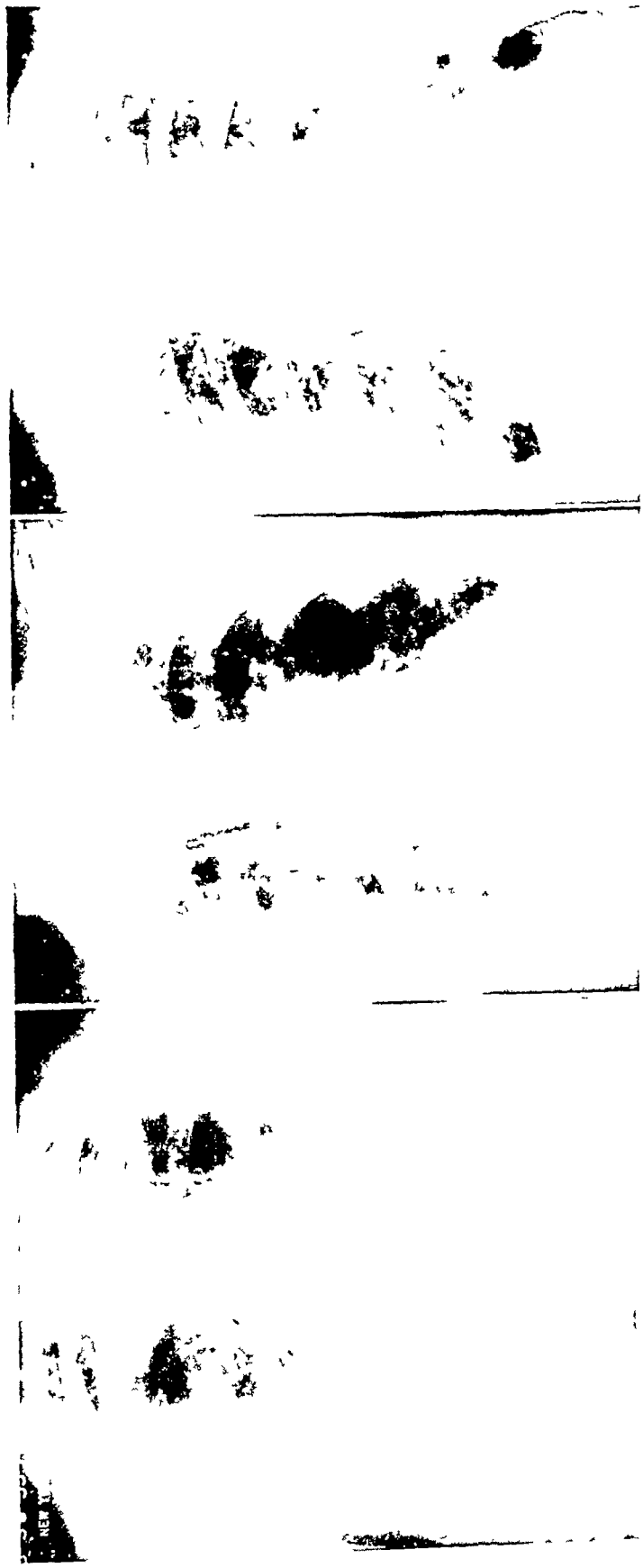


FIGURE 1

FIGURE 2

FIGURE 3

Figure 1 Woman, aged 92, senile lung pattern —*Figure 2* Woman, aged 90, senile lung pattern —*Figure 3* Man, aged 84, senile lung pattern

aged patients Monroe[2] flatly states that emphysema is no more frequent in the aged than in the young Howell[3] states that the hypertrophic type decreases its incidence with age and becomes rare after 70, when "atrophic emphysema" becomes predominant It is quite obvious from the discussion of Howell that his description of the atrophic form in the aged is based entirely on interpretation of morphologic features and bears no relationship to any clinical picture What Howell described as "atrophic emphysema" is in reality what we have defined as "senile lung"

Laennec[4] gave the following description of the morphologic features of the lungs of the aged

"In very old persons the lungs present some remarkable characters The calibre of all their vessels seems diminished, they become in some sort exsanguine, the partitions of their air cells appear thinner than natural, on which account their substance, rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on opening of the body, they are found to occupy not more than one-third of the cavity of the pleura They may be said to bear the same relation to the lungs of an adult, that muslin bears to a finer cloth, which is of a texture at once strong and close These characters are especially observable in the lungs of octogenarians"

This remarkable description of "senile lungs" Laennec included into his introductory chapter on the anatomy and not into his famous chapter on emphysema By this Laennec implied a sharp distinction between emphysema and senile lungs which we believe applies today just as it did then In light of this interpretation "senile emphysema" seems to us to be a misnomer and accounts for the high incidence of alleged emphysema in the aged By the same token the low incidence of true emphysema found by us in this group of aged becomes understandable

The current classification of chronic emphysema into hypertrophic and atrophic forms has led to the trend of identifying these as obstructive and senile forms respectively As both are presumed to occur predominantly in patients of advancing age, the obstructive type is usually explained by long protracted bronchial disease, while the atrophic form is linked to the aging process These concepts have only added to the prevailing confusion, since clinical experience has clearly established certain facts (1) Chronic pulmonary emphysema is not the disease of advanced age that it is generally assumed to be A large proportion of the patients are in the 40 to 60 age group and many are even in the 30s (2) So called "atrophic emphysema' is not uncommonly found in young patients (3) Pulmonary emphysema occurring as a disease in the aged is just as frequently obstructive in character as in the younger age groups

The discrepancy between current beliefs and these clinical facts are readily explained on the basis of our concept of the "senile lung" versus "senile emphysema" We note in recent literature, since our publication on the senile lung, that there is now a definite trend to accept

this interpretation Speaking of the aging lung, Richards[7] most recently emphasized that "the aging normal lung is remarkably adequate and efficient." He discussed a variety of pulmonary conditions now usually spoken of as senile or atrophic emphysema and described these as "pulmonary processes, not aging or senile, but nonetheless truly atrophic and degenerative, that are of importance in the pathogenesis of certain chronic disease stages" The origins of emphysema are still obscure and the terms "atrophic" and "degenerative" do not explain them

What is now described as "atrophic emphysema" occurs in young and old alike and we do not believe it should be identified as "senile emphysema" The problem of the relationship of senile lungs to emphysema proper remains to be clarified A little later we shall return to this question

We found a rather low incidence of clinical emphysema among the aged* This should not come as a surprise, because it is generally recognized by experienced clinicians that the vast majority of patients with chronic progressive emphysema do not reach old age, especially the old age of today Of course, some do survive and the cases of emphysema we found were mostly over age 70 and most of them had a fairly long history of pulmonary disease

Our observations so far indicate that as a rule clinical emphysema does not begin in the aged By this we do not wish to imply that aging plays no role in the progression of emphysema Indeed the contrary may be assumed Chronic emphysema is related to the *exhaustion of pulmonary reserves* by repeated occurrences of a variety of bronchopulmonary diseases

*It should be noted that this group of aged was subject to pre-admission examination and that most of those who were admitted were apparently healthy, hence this should be considered as a selected group

FIGURE 4

FIGURE 5

Figure 4 Man, aged 87, emphysema —*Figure 5* Woman, aged 81, emphysema

during the patient's life As a rule the process is gradual and most patients reach at least middle age before they suffer from the symptoms and signs of pulmonary insufficiency recognizable as clinical emphysema In a few instances the advance is so gradual as to permit some to survive even to age 75 and over

We found the greatest number of "senile lung" changes in women Considering that clinical emphysema is known to occur 5 to 10 times as often in men, the predominance of senile lung changes in the aged woman is noteworthy Special mention should be made of a few observations First the senile lung changes we found occurred mostly above the age of 80, only rarely below this age More women than men reach the ninth decade Furthermore most men over age 80 in this study gave histories of physically active lives and were in fine physical state for their age, on the other hand of the women studied, a large number had never led strenuous physical lives, and progressive aging inclined them to even less activity We inescapably gained the impression that in the aged who had led physically active lives the involutional lung changes were less marked than in those who had not Indeed, enforced idleness seemed in a few instances to have accelerated senile pulmonary changes

From the clinical experience related above, we were led to conclude that functional disuse is probably the most important factor in the pathogenesis of the atrophy of the "senile lung" This conflicts with the prevailing concept of the "atrophy of abuse" which relates emphysema to continued stress on or abuse of the elastic structures of the lungs

Based on our concept of "atrophy of disuse" it seems that a new approach to the therapy of emphysema has been made Recently Bickerman[6] stated "If disuse atrophy plays any part in the pathogenesis of 'senile emphysema,' as has been suggested by Rappaport and Mayer, graded respiratory exercises adapted to the exercise tolerance of the patient will result in clinical improvement and will arrest further deterioration" Accordingly, Barach has been treating emphysema with apparent success employing a program of walking while the patient breathes 10 liters of O_2 per minute, a therapeutic exercise calculated to build pulmonary reserve While accepting our concept of "disuse atrophy," these clinicians apply it to emphysema in general If the reported results of this new therapy prove to be correct they may shed light on the relationship between the aging lung and emphysema

Relative to this we have made some observations indicating that aging may aggravate preexisting emphysematous changes and precipitate the onset of clinical emphysema Particularly among patients who develop clinical emphysema during advanced years we may be dealing with instances where senile lung changes have aggravated the progressive decline in pulmonary reserve In a few patients with marked senile lung changes, we observed the occurrence of an acute emphysema-like syndrome which was precipitated by intercurrent illness associated with respiratory embarrassment Chief among these predisposing factors

were pulmonary congestion of cardiovascular origin, trauma leading to prolonged bedridden state, and a sudden respiratory infection of otherwise harmless nature, such as mild bronchitis In these cases "senile lung" changes may have served to contribute to the evolution of "clinical emphysema" Perhaps in such cases treatment capable of delaying the progress of the senile lung changes could account at least temporarily for improvement in the patient's condition

SUMMARY AND CONCLUSIONS

Preliminary findings in a clinical study of emphysema in aged men and women have yielded substantial support of the validity of our concepts of "senile lung" versus "senile emphysema" Aging is associated with changes which result in the senile lung In our study this change became clinically demonstrable particularly after age 80 and predominantly in women We found it rarely recognizable before that However, not all persons show this change, even at this advanced age In the aged who have led a life of vigorous activity, senile lung changes, particularly in men, appear to be delayed or absent "Atrophy through disuse" probably plays a role in the changes of the "senile lung"

The term "senile emphysema" appears to us to be a misnomer The "senile lung" does not manifest itself clinically as emphysema, nor is the latter a common disease among the aged Clinical emphysema presents the same features in the aged as in the young In aged emphysematous people the clinical signs and symptoms of obstructive breathing are present and the thorax is overdistended In the truly senile state, the chest and lungs show loss of structure and contraction in volume, but their functions appear quite sufficient for these aged people with their reduced activities In some instances "senile lung" changes may predispose to a late and rapid onset of emphysema under such pathologic conditions as congestive failure or bronchopulmonary infections, which tend to increase the functional burden upon the heart and lungs

RESUMEN Y CONCLUSIONES

Los hallazgos preliminares después de un estudio del enfisema en hombres y mujeres de edad avanzada, han dado respaldo sólido a la validez de los conceptos de "pulmón senil" en lugar de "enfisema senil" Al envejecimiento acompañan cambios que viene a constituir el pulmón senil En nuestro estudio este cambio se hizo demonstrable clínicamente especialmente después de los 80 años predominantmente en mujeres Rara vez los reconocimos antes de esta edad Sin embargo, no todas las personas muestran este cambio aún a este edad avanzada En los ancianos que han llevado una vida de vigorosa actividad, las alteraciones seniles, especialmente en los hombres, parecen ser retardadas o ausentes La "atrofia por falta de uso" probablemente desempeña un papel en las alteraciones del "pulmón senil"

El hombre "enfisema senil" nos parece que es mal aplicado El "pulmón senil" no se manifiesta por sí como enfisema, ni es este último una enfer-

medad comun entre los viejos El enfisema clínico presenta las mismas caracteristicas en los jóvenes y en los viejos En los ancianos enfisematosos, los signos clínicos y los síntomas de respiración obstruída se presentan y el tórax está sobre-distendido En el estado senil verdadero, el tórax y los pulmones nuestran pérdidas estructurales y de la contracción del volumen, pero su función parece bien suficiente para estas gentes de edad con reducidas actividades En algunos casos el "pulmón senil" por sus cambios predispone a un principio tardío y rápido en evolucionar del enfisema cuando hay insuficiencia congestiva o infecciones bronconeumonares que tienden a aumentar la carga funcional sobre el corazón y sobre los pulmones

RESUME ET CONCLUSIONS

Les constatations préliminaires d'une étude clinique de l'emphysème chez les personnes âgées ont apporté un argument solide en faveur de nos conceptions du "poumon sénile" par opposition a l'emphysème sénile" La senescence a pour conséquence des altérations qui provoquent le poumon senile Rans notre étude, ces lésions purent être mises cliniquement en évidence, particulièrement après l'âge de 80 ans et surtout chez les femmes On peut difficilement les reconnaitre avant cet âge Cependant, toutes les personnes même très âgées ne présentent pas obligatoirement de telles lésions Chez les vieillards qui ont mené une vie très active, les altérations pulmonaires séniles, surtout chez les hommes, semblent reculer leur apparition ou être absentes "L'atrophie par non-emploi" joue probablement un rôle dans les lésions du "opumon sénile"

Le terme d'"emphysème sénile" ne nous semble pas heureux Le "poumon sénile" ne se manifeste pas cliniquement comme un emphysème, cette dernière affection n'étant d'ailleurs pas une maladie commune chez les gens âgés L'emphysème clinique présente les mêmes caractéristiques chez les personnes âgées que chez les jeunes Chez les gens âgés emphysemateux, les signes cliniques et les symptômes d'obstruction respiratoire existent et le thorax est distendu Dans la véritable condition sénile, le thorax et les poumons se présentent avec une diminution de leur texture et avec une contraction de leur volume, mais leurs fonctions semblent cependant suffisantes pour ces personnes âgées dont l'activité est réduite Dans quelques exemples, les altérations dues au "poumon sénile" peuvent prédisposer à l'établissement ultérieur et rapide de l'emphysème à l'occassion de conditions pathologiques telles que les troubles congestifs et les infections bronchopulmonaires, qui tendent à augmenter le retentissement fonctionnel sur le coeur et les poumons

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Vorlaufige Ergebnisse einer klinischen Untersuchung uber das Emphysem bei betagten Mannern und Frauen ergab eine wesentliche Bestatigung fu die Stichhaltigkeit unserer Auffassung von der "senilen Lunge" gegenuber dem "senilen Emphysem" Das Altern ist verknupft mit Veranderungen, deren Ergebnis die senile Lunge ist Bei unserer

Untersuchung liessen sich diese Veranderungen klinisch nachweisen besonders nach einem Alter von 80 Jahren und in erster Linie bei Frauen Wir fanden, dass sie selten zu erkennen sind vor diesem Zeitpunkt Jedoch zeigen nicht alle Personen diese Veranderung, selbst nicht in so vorgerucktem Alter Bei solchen bejahrten Menschen, die ein Leben tatkraftiger Aktivitat gefuhrt haben, scheinen senile Lungen-Veranderungen, besonders bei Mannern, zu fehlen oder verzogert aufzutreten "Atrophie durch Nicht-Gebrauch" spielt wahrscheinlich eine Rolle bei den Veranderungen der "senilen Lunge"

Die Bezeichnung "seniles Emphysem" scheint uns eine falsche Benennung zu sein Die "senile Lunge" manifestiert sich klinisch nicht als Emphysem, noch ist das letztere eine haufige Erkrankung unter alten Menschen Das klinische Emphysem biete die gleichen Eigenheiten im Alter wie in der Jugend Bei alten emphysematosen Menschen liegen die klinischen Zeichen und Symptome der stenotischen Atmung vor, und der Thorax ist uberdehnt Beim echten senilen Status zeigen Brustkorb und Lungen einen Verlust an Struktur und Kontraktion des Volumens, aber ihre Funktionen erscheinen vollig ausreichend fur solche alten Menschen mit ihrer herabgesetzten Leistungsbreite In gewissen Fallen konnen die Veranderungen einer "senilen Lunge" praedisponieren zu einem spaten und raschen Beginn eines Emphysems unter pathologischen Bedingungen so wie Herzversagen durch Stauung oder bronchopulmonale Infektionen, denen die Tendenz inne wohnt, die funktionelle Belastung fur Herz und Lunge zu vermehren

REFERENCES

1 Rappaport, I and Mayer, E "Emphysema and the senile lung," *Jrl Amer Geriatrics*, 1954
2 Monroe, R T "Diseases in Old Age," Cambridge, *Harvard Univ Press*, 1951
3 Howell, T H and Piggott, A P "Morbid anatomy of old age," *Geriatrics*, 6 85, 1951, 8 267, 1953
4 Laennec, R T H "A Treatise on Diseases of the Chest," ed 3, translated by John Forbes, New York, *S & W Wood*, 1838
5 Richards, D W "The aging lung," *Bull N Y Academy Medicine*, 32 407, 1956
6 Bickerman, H A "Chapter on senile emphysema in Pulmonary Emphysema," edited by A L Barach and H A Bickerman, *The William & Wilkins Co*, Baltimore, 1956
7 Barach, Alvin L "The treatment of pulmonary emphysema in the elderly," *J Geriatrics, Soc*, 4 884, 1956

Pathologic Findings in Benign Pulmonary Histoplasmosis*

Preliminary Report—Part II†

HENRY C SWEANY, M D, F C C P,** DAVID GORELICK, M D,‡
FRED C COLLER, M D‡ and JAMES L JONES, H T§
Mt Vernon, Missouri

Another case will be given where the fibrosis was extremely heavy—sometimes the cavity walls measured 2-3 cm in thickness

S R B 10 No 23,637 The patient was a 58 year old housewife of New Madrid, Missouri She gave a history of "virus pneumonia" in 1951 lasting two to three weeks Following this she complained of gastric disturbance and was examined for gall bladder disease but an x-ray of the chest caused the private physician to make a diagnosis of tuberculosis and recommended admission to the hospital for treatment The x-ray film revealed a dense infiltration throughout the right lung field with multiple areas of cavitation No sputum examinations were recorded up to this time

In January 1953 there was another attack of "virus pneumonia" and the patient was admitted to the hospital on February 23, 1953 At this time she gave a history of malaise, loss of weight (13 pounds), cough which was sometimes productive, and once in February 1953 the sputum was streaked with blood In addition there was anorexia, nightsweats and fever There had been a recurrence of the gastric symptoms with pain in the right upper abdomen but a complete gastro-intestinal workup revealed nothing The right upper lung field was as previously described On admission there was a dyspnea, temperature of 99 4, pulse of 120, and respiration of 20 The gastro-intestinal symptoms had disappeared by this time

The physical examination was essentially negative except for the chest where there were many fine rales on auscultation in the right upper half and mid lung field (Figs 36 and 37)

The laboratory examination revealed a completely negative tuberculin test, fourteen consecutive negative sputum examinations for acid fast bacilli even though there was an expectoration of 40 to 50 cubic centimeters of purulent to mucopurulent sputum Two cultures of sputum were also negative for acid fast bacilli

Three bronchoscopic examinations for acid fast bacilli were negative on smear and culture as well as for cancer cells Six sputums were also negative for cancer cells Due to a fluctuating temperature a therapeutic trial of one gram streptomycin three times a week and twelve grams of PAS daily was begun on April 1, 1953 The temperature receded from around 101 degrees to near normal after the antibiotics were given but around July 1, 1953 streaking of the sputum was noted again and a pneumoperitoneum of 700 cubic centimeters was begun on July 4, 1953 At this time 400,000 to 800,000 units of penicillin was administered

Despite the slight clinical improvement in March there was a progressive increase in symptoms, her general condition declined and the x-ray films showed a progression of the disease At this time the skin test for histoplasmosis was found positive but the skin test was negative for blastomycosis and coccidioidomycosis Serum was sent to Dr Fulcolow for complement fixation test which was reported positive on August 1,

---

From the Missouri State Sanatorium We are deeply indebted to Dr Charles A Brashear, Medical Director, for unreserved support in this work

It was the privilege and pleasure of one of us (S) to be accorded the courtesy of members of the Armed Forces Institute of Pathology, in Washington, D C, where many valuable suggestions were made that helped to orient us in our studies We are particularly grateful to Capt Silliphant, Director of the Institute, and to Dr S H Rosen, of the Pathological Department of Chest Diseases

**Director of Research, Pathology and Allied Sciences

†Presented in brief before the Chicago Pathological Society, May 13, 1957, and in full at the Am Soc Clin Path at New Orleans, Oct 2, 1957

‡Consulting Pathologist

§Histological Technician

A few specimens were from the Pathology Department of St John's Hospital and Springfield Baptist Hospital, Springfield, Mo, where D G and F C are pathologists

1953 In view of the fact that the tests for histoplasmosis were positive and all other tests were negative, the diagnosis pointed to histoplasmosis Sputum cultures were ordered for Histoplasma capsulatum and on August 20 and 26, 1953, Dr Furcolow reported positive growth of that microorganism on culture media and the development of disease in mice after inoculation with concentrated sputum At a later time many positive cultures were obtained

In view of these findings she was brought to the conference on August 9, 1953 and an exploratory operation was recommended Accordingly on September 25, 1953, complete pneumonectomy was performed by Dr Polk and his assistants

A pathological report was as follows The gross specimen consisted of resected right lung which weighed 520 grams and had been fixed in formalin The upper half presented marked thickening of the pleura and had been resected with attached parietal pleura In some places the pleura measured 2-3 cms in thickness and had a dense fibrotic make-up which in some places had the consistency of cartilage On section all the upper half of the lung presented an intercommunicating irregular cavity The inner surface was rather smooth, grayish in color and transversed by obliterated thrombosed blood vessels and cords of broken-down bronchi The wall of the cavity was light gray with areas of anthracotic deposition and the tissue everywhere was very dense Beneath the lower margin of the thickened pleura there was revealed several patent fistulous openings which communicated with the cavity There were numbers of enlarged peribronchial and hilar lymph nodes which generally were of gray to black color with only occasional tubercle-like formation around the periphery There was a 1 cm sized, rather thin-walled cavity in the base of the lower lobe which contained purulent grayish colored exudate On section of the rest of the lung the parenchyma was doughy in consistency but presented no grossly demonstrable lesions (Figs 38 and 39)

Microscopic examination of a number of sections from the tissue bordering on the large cavity in the upper lobe revealed no functional lung parenchyma The area lining the cavity presented on inner aspect, much cellular detritus and degenerating reactive cells of various types This over-lay an area of acidophilic staining hyloid material in which there were relatively few reactive cells and the true nature of which was not apparent Just beyond this there was a mixed chronic type of cellular reaction which was made up mostly of plasma cells fibroblasts, mononuclear macrophages and also a few multinucleated foreign body giant cells Beyond this area there was

FIGURE 36

FIGURE 37

Figure 36 (A) Roentgenogram of S R, B10, No 23,637, taken on August 21, 1953 Note destroyed right upper lobe.—*Figure 37* (B) Sagittal section of upper lobe of lung removed on September 25, 1953, showing extremely thick-walled cavities with no pyogenic membrane

rather compact fibrocystic reaction in which there were foci of chronic reactive cells and also among which there were regenerating alveolar and bronchiolar structures Occasionally a single and conglomerate tubercle-like formation was observed within this area and the reactive components of which were usually of fibrous and epithelioid cells as well as one to several multinucleated foreign body giant cells Occasionally within the giant cell there was observed an irregular shaped refractile body which morphologically appeared to be a foreign body rather than ingested bacteria In two sections

FIG 38

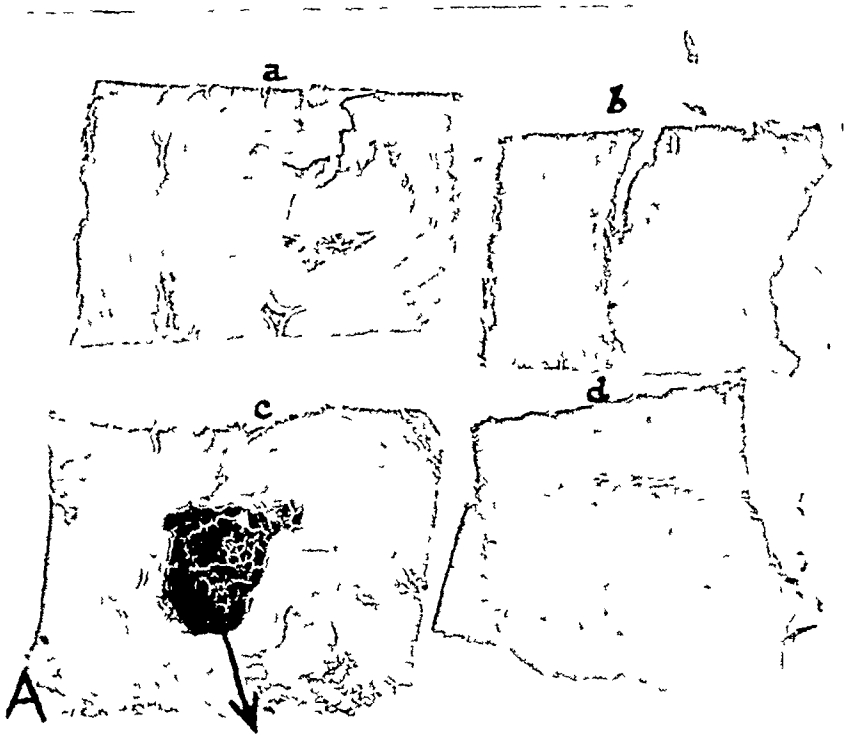


FIG 39

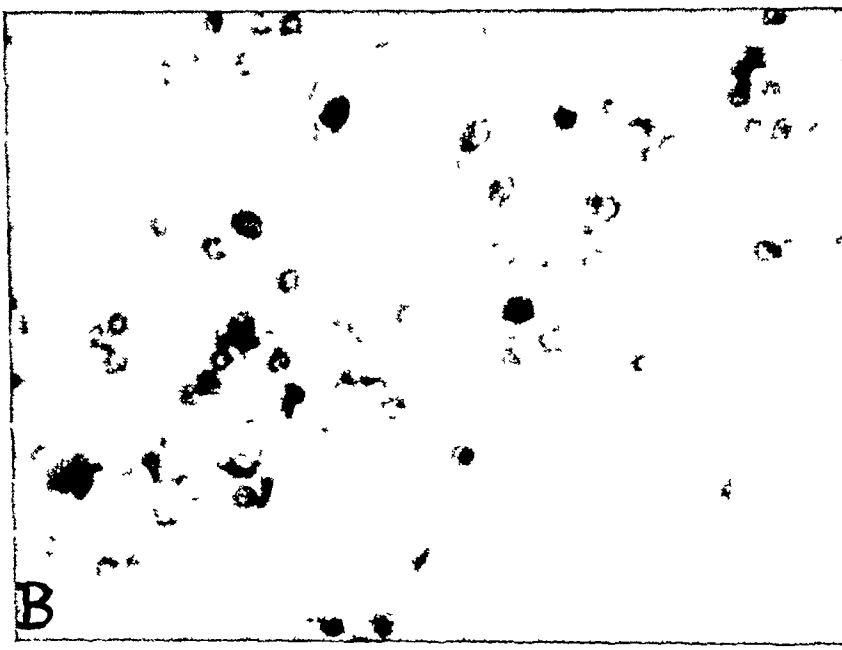


Figure 38 (A) Sections "a," "b," "c," "d," made from encapsulated lesions removed and stained in 1956 H & E × 4 5—*Figure 39* (B) Microscopic photograph of yeast bodies found in the "c" lesion of Fig 38 G M S stain × 3200

there were observed secondary bronchi which presented thickening of their walls secondary to marked secondary chronic inflammatory reaction In two there was definite erosion of the bronchial mucosa and extension of the inflammatory reaction into the submucosal levels The lesion was definitely of granulomatous type but not typical of mycobacterial infection Sections of accompanying lymph nodes showed in two, several fibroepithelioid tubercle formations in which there were from one to several multinucleated foreign body cells of the same type seen in the lung lesions The lymphoid stroma otherwise was moderately hyperplastic No inclusion bodies of the Histoplasma type were observed within the reactive cells

Cultures initiated from the lung lesions presented colonies which were morphologically suggestive of Histoplasma capsulatum Acid fast stains and PAS stains did not demonstrate the presence of Microbacterium tuberculosis or any fungal organisms Diagnosis Right pneumonectomy for chronic cavitary granulomatous pneumonitis caused by Histoplasma capsulatum based on bacteriological and serological findings

Due to the uncertainty of the staining methods used up to this time, a complete re-examination of the gross and microscopic specimens was made in January, 1957 Since the special stains used did not reveal any typical findings of H capsulatum and since the more recent observations and technical advancement had changed the method of approach in examination, the gross specimen was re-examined for encapsulated caseous and calcified foci, cut and stained by the G M S technic About four encapsulated lesions were removed and examined for yeast The result was the finding of a large number of yeast bodies typical of H capsulatum in most of the specimens as well as a few forms in the wall of the cavity

This completed the search for the etiological agent and established the fact that every test for the presence of histoplasmosis was positive and practically every test for other conditions was negative

The final diagnosis was, therefore, acute and chronic fibro-ulcerative, fibrocaseous nodular and infiltrative histoplasmosis

It is worth noting that after two re-admissions to the hospital and re-examinations, the patient has up to now, July 1957, not revealed any exacerbation of her disease This is five years after her operation

A sixth group was bronchiectasis Although bronchiectasis may be caused by many infectious agents, histoplasmosis may be one of these agents, as shown in one of the cases In one case a culture of H capsulatum was obtained from a specimen of the bronchial wall Everything else was negative, but because of this positive culture a careful search was made of the tissue and every encapsulated lesion was excised and stained by the G M S stain Many parasites were found in the encapsulated lesions but only a few were found in the wall of the bronchiectatic cavity Once again it showed the predilection of these parasites for encapsulated caseous foci A more complete report on bronchiectasis will be given in a separate study

The seventh group may be considered as a pleuritic involvement with effusion, not greatly unlike that seen in tuberculosis There was one case in which the effusion contained Histoplasma capsulatum, and without the presence of the parasites it could not be distinguished from tuberculosis

Finally, there was a mixed up group that includes many of these various types of lesions because in practically every case two or more of these various types of pathology could be found There were sometimes calcific, and chronic fibroid lesions associated with acute caseous foci and with cavity formation In most of the chronic forms there were found encapsulated caseous foci in which numerous parasites were found It may be stated that there was nothing found that simulated microscopically the tuberculous caseous pneumonia

Probably one of the most difficult distinctions—in fact, impossible without the parasites of both diseases—is to tell when tuberculosis and histoplasmosis exist together In four cases, tuberculosis was diagnosed first

because of the acid-fast bacilli, but after long drug treatment the disease continued after the acid-fast bacilli had long since disappeared Since this combination is so important, the four cases will be briefly summarized

A R W, B 6, was a 35 year old painter The skin test was strongly positive for histoplasmosis and the tuberculin skin test was weakly positive The complement fixation was weakly positive with one antigen and negative with the other Sputum smears were positive for acid-fast bacilli on numerous occasions All cultures and mouse inoculations were negative for histoplasmosis The sputum smears finally turned negative for tubercle bacilli, after which a surgical resection was performed On the P A S stains of prepared sections there was granulomatous tissue present with many histiocytes containing many suspicious "cherry colored" bodies These were not considered diagnostic of histoplasmosis, but when four or five typical forms that showed birefringence were found on the Gomori stain, the diagnosis of histoplasmosis was made Segmental resection of the left upper and wedge resection of the lingula removed all apparent disease up to the present time

E S, B 15, No 23,056, was a 50 year old truck driver The skin reaction was weakly positive for histoplasmosis and strongly positive for tuberculosis The complement fixation was weakly positive At the beginning all sputum smears were positive for acid-fast bacilli, but turned negative and remained negative, yet the disease continued until the whole left lung was destroyed Pathological findings revealed a typical appearing primary type of tuberculous lesion, however, it was called a reinfection complex on gross inspection On microscopic study, the lesions contained many bony rings and appeared more like a true primary tuberculous complex In these lesions were many yeast bodies that pointed strongly to a primary complex of histoplasmosis This case seems to represent, therefore, a very old histoplasmosis that was superimposed with tuberculosis, and the two diseases ran parallel until the drug treatment seemed to limit the progress of the tuberculosis, and the surgery ended the threat of both diseases, temporarily at least

O W, B 24, No 25,388, was a 58 year old farmer with a weakly positive skin test for both histoplasmosis and tuberculosis There was a strongly positive complement fixation test with both antigens Six sputum smears were positive for acid-fast bacilli, but after a course of drug treatment, the acid-fast bacilli disappeared from the sputum Numerous cultures were positive for histoplasmosis and the complement fixation continued positive, many times as high as 1 256 dilution The whole right

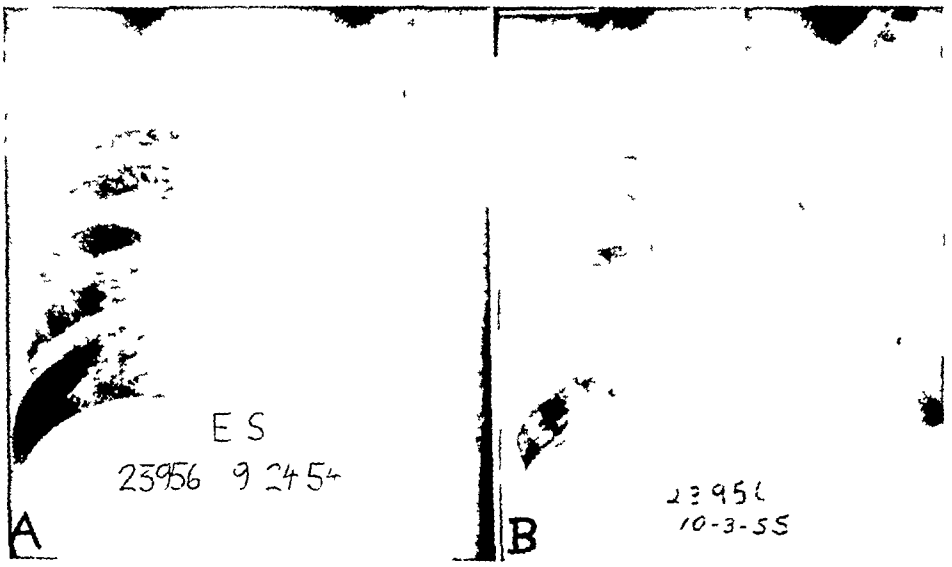


FIGURE 40

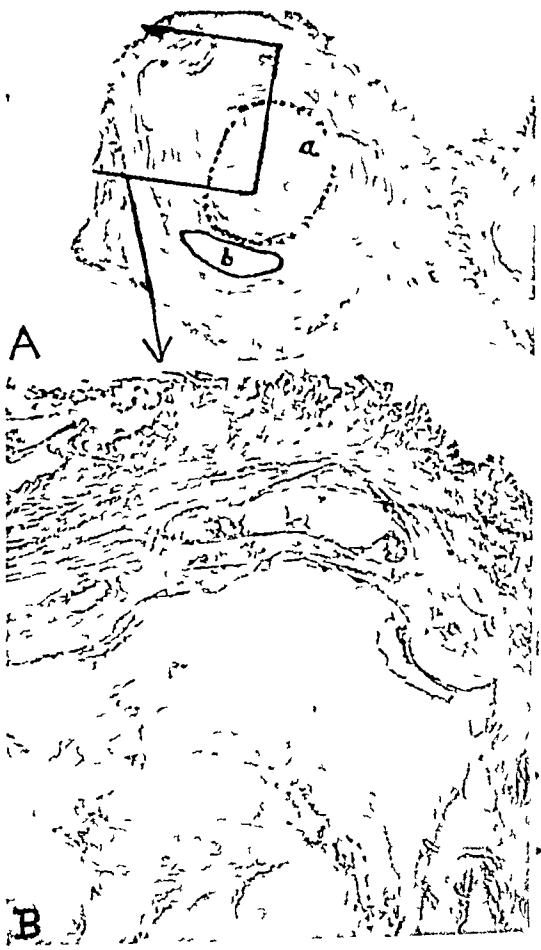
FIGURE 41

Figure 40 (A) Roentgenogram of E S, B15, No 23,956, taken on September 24, 1954, showing a consolidated left lung—*Figure 41* (B) The same as Fig 38, taken on October 3, 1955 with a double exposure to show the nature of the lesion on the left This patient was always positive for a f b and turned negative on antituberculosis drugs

upper lobe was destroyed and contained a large cavity A surgical resection was successful, but the patient died later of a coronary thrombosis The pathological findings consisted of a cavity wall that was more typical histoplasmosis than tuberculosis There were scattered yeast bodies throughout the cavity wall and in some of the caseous foci, but since no encapsulated lesions were found, the large accumulations of parasites found in so many of the other cases were absent The reaction was histiocytic, not granulocytic This case was one in which the two diseases seemed to run parallel, but the tuberculosis was suppressed, either by drugs or by the histoplasmosis The surgery was successful and the death was in no way caused by either disease, or by the operation

R H, B 25, No 25,465, was a 33 year old janitor with a positive skin test for both histoplasmosis and tuberculosis The complement fixation was positive with both antigens The sputum smear was positive during the early stages of treatment for acid-fast bacilli All cultures for histoplasmosis, both sputum and pathological specimens were negative Birefringent yeast-like bodies were found on the Gomori stain The two diseases were both present in this case, but the acid-fast bacilli disappeared first, either due to the drug treatment, or to the histoplasmosis A wedge resection of the left upper lobe and a decortication of the left pleural cavity was successful and the patient made an uneventful recovery

FIG 44 FIG 45



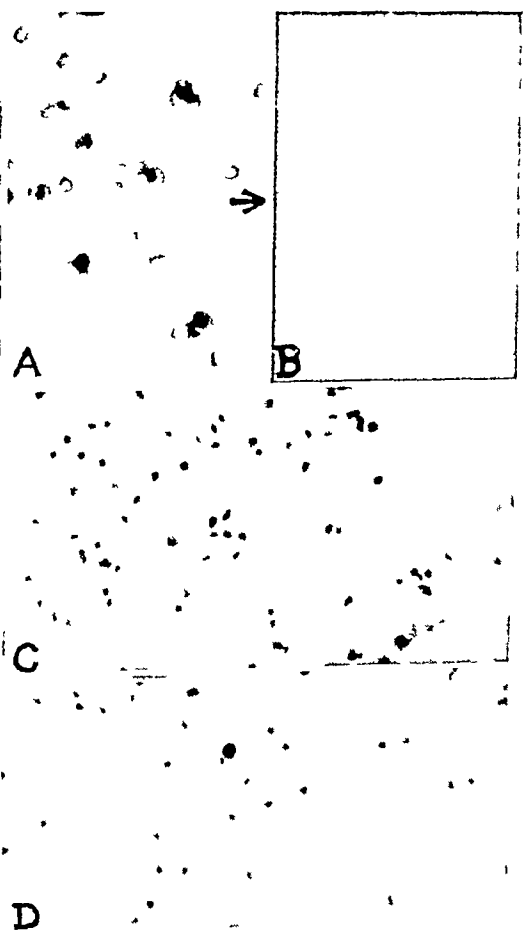


FIG 42

FIG 43

FIG 46

FIG 47

Figure 42 (A) A low power view of a section of a dense parenchymal calcification taken from the resected left lung of patient shown in Figs 38 and 39 Two areas are outlined in the center of the lesion, one by dots at "a," and another by black line at "b" H & E × 45—*Figure 43* (B) A squared-off area of Fig 36 showing bony character of lesion H & E × 20—*Figure 44* (A) A microscopic view of region marked at "a" in Fig 40, showing numerous typical yeast bodies G M S stain × 3200—*Figure 45* Polariscopic view of Fig 42 × 3200—*Figure 46* (C) A view of field marked off at "b" in Fig 40 Note the numerous small dark staining bodies that may be developing into yeast bodies G M S stain × 3200—*Figure 47* (D) Another view of the field of "b" in Fig 40 G M S stain × 3200

Another condition that may be simulated by histoplasmosis is sarcoidosis It must be pointed out, however, that the finding of parasites in a sarcoid-like lesion does not rule out sarcoidosis, nor does it imply in any way that histoplasmosis may be the cause of sarcoidosis Since the normal expectancy we found in this region of tuberculosis in the presence of active histoplasmosis is 25 per cent, that same percentage at least may be expected in sarcoidosis, Hodgkin's disease, lymphomas, or any other similar involvement In three cases, however, of proved sarcoidosis, yeast bodies were not found

It must not be inferred either that the ratio found here will be found elsewhere, especially in places where the histoplasmosis is not endemic An examination of some of the old tubercles studied many years ago by one of us (S) in an area low in incidence of histoplasmosis has revealed no H capsulatum in a large number of the stained sections

Another condition as briefly mentioned that may be produced, is bronchiectasis Histoplasma capsulatum may be the inciting agent, like many forms of bacterial infection and other conditions leading to bronchial stricture that results in bronchial dilatation and the accumulation of pus in the sacs formed In such lesions there is much non-specific reaction

Discussion

Although we have attempted to describe the gross and miscroscopic lesions found in our material as consistently as possible, it is evident that there are still gaps in the pathology of the disease that probably were not found For example, it is highly probable that many lesions are primary infections with the parenchymal infiltrates and lymph node involvements like those found in tuberculosis Such lesions, however, would be easier to study during the early stages of the infection Many of the calcified lesions may have been old primary lesions, but with two exceptions only the parenchymal components were excised so we wouldn't be certain of the complete pathology Ulcerative bronchitis was not found in any of the histoplasmosis cases, although growth into the bronchi of one case was found Hematogenous dissemination in the lungs was not found There probably are other conditions also that were not represented in our material

One of the big problems, in fact, the most important problem, is establishing a diagnosis of histoplasmosis Owing to the fact that the disease simulates tuberculosis, sarcoidosis, and other diseases so closely, clinical and x-ray findings are of limited value With the possible exception of the history, such as occupation and geographic location, clinical and x-ray findings are at no time conclusive The skin reactions and complement fixation are sometimes helpful In an endemic area, especially if the individual has been working around decayed and drying organic material such as chicken and pigeon manure, silos or dry dust, and if there is a strong positive skin reaction and strong complement fixation for histoplasmosis with negative tuberculin, there is strong presumptive evidence of histoplasmosis Negative findings, however, of any or all of these indicators

do not rule out the disease The only absolute diagnosis is when a typical culture of the parasite is grown on some or all of various media and when animals are infected and die with the disease Even under the best of circumstances, however, culture and animal inoculation is only about 50 per cent efficient up to this time in the type of case we have been dealing with The complement fixation proved to be erratic, since in three clinically positive cases the reaction was negative, and many positives did not have any parasites on culture or in the tissues examined Salvin[16] suggested that there were at least three antigens It has been shown that the complement fixation antibodies appear best at the height of the acute disease and that they tend to fade in chronic forms and almost entirely disappear in fulminating cases McLaurin, Beamer and Tuttle[17] have shown that there is not a single antigen, but there is a difference between the whole yeast antigen and the mycelial antigen

The skin reaction persists much longer It is more useful, except where the complement fixation is present in high dilutions or the tuberculin positive

The staining of tissues is one of the best means of establishing a diagnosis There has been marked progress made in this field recently Although the H and E stain is standard for almost every histopathological method, it stains the yeast parasites little or not at all, and more important, there are calcific rings that simulate the parasite closely Unless there is an overwhelming infection with large numbers in the macrophages, the parasites will be missed Although the PAS stain with various modifications was a considerable advance, there is much the same objection to it as to the H and E stain When the macrophages are packed with the parasites rather early in the disease, they may be distinguished easily by the cherry-colored nuclear material surrounded by a capsule which usually stains a similar color There were no more than four of our cases, however, which we felt with none too much certainty were H capsulatum based on the PAS stain One of the principal artefacts that simulate these bodies is the early stage of hemosiderin formation, when the hemosiderin becomes phagocytized in small clumps and appears very much like the parasites Although there are many substances in the tissues that stain with the PAS stain, most of such artefacts can be separated from anything that resembles the parasite of histoplasmosis

The Gridley stain has eliminated many of these extraneous factors, but it still is lacking in being able to identify the parasites with regularity

It should be kept in mind, that a diagnosis of many conditions including tuberculosis may not be definitely established If artefacts or inadequate findings lead to a diagnosis of histoplasmosis in the absence of other findings, who can dispute the diagnosis? Many "diagnoses" have perhaps been made on artefacts That is the reason why great care and definite proof must be found before a diagnosis is made Furthermore, it must be pointed out that parasites are not always found either in tuberculosis or histoplasmosis Perhaps the average results are not higher than 90 per cent when only *one* section is examined, because one section represents much

less than 1 per cent of each round lesion Our results were only about 82 per cent

The methenamine silver stain of Gomori which was originally intended as a glycogen and mucin stain, but was used in identification of yeast parasites by Grocott, has been found to be the best of all tissue stains for identification of H capsulatum and many other yeast and mold parasites It is especially useful in identification of H capsulatum because most of the other yeasts and molds may be identified by some of the other stains

In performing this test it is well to remember that perfection of technic is most helpful The purity of the chemicals, the timing of the exposure to these chemicals, together with a well regulated temperature is necessary for good results It is well for each operator to develop his own technic with great precision and run good control stains for comparison The procedure may be compared to expert photography in bringing out desirable features

As a method of control of the various forms adjudged to be yeast bodies, we made use of the polariscopic attachment of the Leitz Dialux microscope to test the birefringence of the parasites A description of the use of the polariscope in identifying birefringence in the various yeasts has been given by Potenza and Feo [18] We used this polariscope method after finding the bodies stained by Gomori's method

It must be pointed out, however, that this is not absolute either, because it is dependent upon proper staining and the presence of the polysaccharide which is reduced to the aldehyde and which in turn reduces the methenamine silver to metallic silver A more complete discussion of this method will be given at a later time, but it may be stated here that there are numerous artefacts that have to be considered and eliminated, much like the staining of tubercle bacilli with the acid-fast stain We feel, however, that the Gomori (G M S) method compares as favorably in histoplasmosis as the acid-fast stain does in tuberculosis, especially when all the control methods are carried out and when checked by the polariscopic findings

It appeared to us that we were able to follow the disintegration of the macrophages and the parasites they contained, better with the Gomori stain than any other Nevertheless, as the disintegration progressed the small black bodies that perhaps represented the parasites seemed to become smaller There came a time when it was impossible to tell these bodies from carbon and iron pigment We were impressed with the possibility that most of the parasites appeared to be destroyed by the macrophages, but after the macrophages themselves became destroyed some of these small spore-like bodies or residual nuclear portions of the parasites still may have retained life, and after months, and even years, began to grow in encapsulated caseous and calcified foci Otherwise, how could a growth occur in a densely encapsulated and calcified lesion?

Another thing was that the evolution of these granules seemed to progress from approximately one micron in diameter or even less, according to standard measurement, through various sizes, up to the usual size of three to five microns Birefringence could rarely be identified in any forms

less than one micron in diameter, but a few cases showed birefringence in forms approaching 0.5 μ in diameter. In a subsequent study birefringence was found in forms of 0.3 -0.4 μ in diameter indicating the presence of a polarizing substance.

There are other reasons for suspecting that this "underground" aspect exists. As mentioned before, a well encapsulated lesion is practically impervious to outside elements. Only ions can penetrate the capsule, but no blood elements or parasites such as H. capsulatum can enter until blood vessels penetrate one or more decades later. Yet in all well encapsulated calcified and even ossified lesions of the series, parasites were found almost exclusively in the central caseous and calcified area and rarely in the area where the capillaries have penetrated and eroded away the capsule and laid down bone and bone marrow.

After an unknown interval of time, the small black granules appear to enlarge and increase in numbers reaching sizes up to 3 or more microns, clusters appear, and finally large numbers of vigorous yeast forms appear in the depth of the heavily encapsulated caseated and calcific nodules.

Numerous other artefacts than those mentioned have bothered us considerably, but we have been able to overcome most of them. Such things as fat droplets, lipoid bodies, and degeneration vacuoles can be eliminated with experience. Various crystalline substances which cause birefringence have also interfered with the polariscopic examination, especially in the unstained specimens. We found that the methenamine silver seemed to destroy most of the crystals that cause interference. Checking the typically egg-shaped yeast bodies with birefringent characteristics shown on the polariscope, especially if there was a typical "Maltese Cross" formed, came about as near to establishing the presence of H. capsulatum as anything outside of growing the parasites. Besides it will find about 40 per cent more positives than the present culture methods.

It is our feeling that about 10-15 per cent of the cases were histoplasmosis but we are unable to find the yeast bodies in the material studied. It is sometimes quite difficult to find the parasites in some cases and then there may have been only a few. In a few cases they were never found. One thing certain is that caseation seems to be the indispensable medium for the propagation of the yeasts in encapsulated lesions. It seems reasonable to suspect that some irritant causes the expanding of the circumscribed lesions, but unless a caseous focus develops no parasites are demonstrable. It is also possible that the parasites may be present in forms that we have not yet been able to recognize. The complete evolution of the parasites is not yet known and until then we must speculate especially with regard to the small spore-like bodies that seem to develop in the caseous areas. In some cases even after several sections at different levels of the block, typical yeast bodies were not found but it must be considered that in a 2 cm. lesion a 6 micron section is only about 1/2000ths of the whole specimen. In none of the specimens therefore did we examine more than 1/10th of one per cent of the total specimen saved.

There are still many unknowns in the histoplasmosis problem, and many

needs that must still be supplied First of all is regarding the culture medium which in our material only grew at the maximum about fifty per cent of the known positive specimens Another need is to explore the evolution of the parasite within the lesions of the body There seems little doubt from studying this material carefully that the yeast form undergoes a change as the macrophages engulf the yeast and apparently destroy them But by the silver stain there are many small blue-black dots that remain in these old destroyed phagocytes It is reasonable to suppose that these bodies may be microspore formations that lie dormant for long periods of time after they are entrapped within the central part of a lesion and remain there for months and years before they are able to develop back into the typical yeast formations A series of transition forms have been followed in all but a few of the cases, from these small blue-black dots through to micron size round bodies up to the typical yeast-like forms which become unmistakable from one and one-half microns on up

While it is not intended to give any extensive clinical findings there are some that may be mentioned in passing Pneumonia was quite frequent in our series of cases and it usually was diagnosed virus pneumonia because there was apparently no microorganisms found Another thing was the vague and indefinite gastrointestinal complaints, sometimes referable to the liver and gall bladder and other times to the stomach There were several ulcers of the stomach that were excised Whether that had any relationship to the tendency to develop histoplasmosis is, of course, not determinable at this time In the cases that we have reported we have found the histoplasmin skin test of greatest value outside of culturing and staining the microorganisms The complement fixation test is dependable in the higher dilutions where it is considered to be diagnostic Among the patients that we have described in our series of cases, chicken raising or farming of some kind where chickens have been raised has been a common denominator in many cases

In retrospect, it seems that the disease of histoplasmosis is one that parallels tuberculosis very closely, although there are differences which have been mentioned but which will not be discussed at this time There is apparently elaborated a toxic substance that produces the skin reaction in infected people, as well as antigens that produce complement-fixing antibodies It is possible that there are more than one of these antigens and that they may differ qualitatively and quantitatively under different circumstances and at different times That may help to explain the erratic findings of the complement fixation reaction in this resected material

In general, histoplasmosis seems to be much more benign than tuberculosis, but in susceptible people with depressed resistance due to malnutrition, other disease, infancy, old age, or overwork, the disease may develop in varying degrees of acuity and produce pathology, some of which we have attempted to describe From our present vantage point it would seem that the disease would yield to methods of treatment more readily than tuberculosis, but that parasites are more prone to survive in encapsulated lesions

It is important to realize that only a small minority of the lesions ever produce active disease, although it appears that histoplasmosis has a long carrier state resembling syphilis, malaria and tuberculosis At this time it appears that in an endemic area such as ours, the incidence of clinically active histoplasmosis is a great many times less than tuberculosis The ratio will probably change, however, as tuberculosis decreases, since there is no way at present to control the spread of histoplasmosis as there is tuberculosis

A question might be raised with reference to length of time the parasites may live in old lesions In one very old lesion no budding and only the faintest birefringence could be detected in rather poorly stained parasites In another case the parasites could be followed through faint staining to mere outlines or ghosts It is felt that the point of viability has passed when budding ceases, staining fades and birefringence disappears Whether any "spore" forms may exist to perpetuate these forms is not always evident Recent and unpublished data reveal much more information on this subject

A word should be said here relative to culturing of H capsulatum With the latest technic in two laboratories, only 50 per cent of the known cases of histoplasmosis in our material produced growth on culture media or disease in mice *

SUMMARY

A preliminary report has been made on the pathologic findings of proved histoplasmosis in 21 circumscribed lesions and sixteen clinically active lesions In addition, there were three doubtful cases in each group that were thought to be histoplasmosis, but in which no typical parasites could be found

There were 24 more specimens examined in which histoplasmosis was not found These served as good controls because they included principally tuberculosis, in which acid-fast bacilli were found and three cases of bronchogenic carcinoma They were included because of the close similarity in clinical, x-ray or other findings to histoplasmosis

There were four clinically active cases with both acid-fast bacilli and H capsulatum.

In addition, three cases of known sarcoidosis as well as many controls of other diseases were stained and examined, but parasites were not found

There were two series of cases, one including apparently inactive disease of so-called "coin" lesions and the other consisting of clinically active disease

The pathologic findings were as follows Group one, centrifugally formed spherical lesions, Group two, encapsulated infiltrates, Group three, caseous nodular lesions resembling caseous tubercles from 1 to 15 milli-

*We wish to extend our thanks to Dr Michael L Furcolow and Dr Howard W Larsh and their assistants at the U S Public Health Service Field Station Laboratory at Kansas City, Kansas, for complement fixation results and for making the cultures during the early part of this study, as well as helping to establish our Mycological Laboratory Also to Dr Joseph Guasch for valuable assistance with the photographic work and to Mr Robert Shackleford for helping in preparing sections

meters in diameter and fibrocaseous calcific and calcific-ossified lesions, the fourth group was chronic pneumonitis which is thought to be divided into several phases of age development from the histiocytic infiltration and early organizing fibrinous pneumonia with histiocytes, to the late granulomatous-type of lesion that simulates sarcoidosis, Group five were the ulcerative types which are divided into caseo-ulcerative (an advanced stage of the caseo-nodular) and the fibroid type of lesions, which ranged from thin-walled, cystic, moderately thick-walled to thick fibrous-walled cavities, the sixth group was pure bronchiectasis that cannot be distinguished in appearance from any other bronchiectasis, but which was found to be a result of infection by H capsulatum, Group seven was the pleuritic-type which is due to invasion of the pleura by H capsulatum, an eighth group was a mixture of two or more of the others

In preparing to make the examinations on this material, an exhaustive study was made of many types of artefacts which were removed or identified by special stains wherever possible

The stain found best for staining yeast bodies was the Gomori methenamine silver (G M S) stain as adapted to the identification of yeast by Grocott

Of the 16 definitely positive active cases, 14 were cultured and/or inoculated into mice, but only seven were found positive

The findings were confirmed where possible by the use of the polariscope, as recommended by Potenza and Feo While not diagnostic it does show the presence of a polarizing substance, probably a polysaccharide

A theory was advanced for the possible evolution of the parasites in the body from the phagocytized cells in the macrophages to a quiescent spore-like form in the fibroid tissue and later a re-awakening of these spore-like forms (endospores) into active yeast cells at a time varying from months and years to decades A further elaboration of these possibilities will be carried out in a subsequent work where more discussion will be possible

RESUMEN

Se presenta una comunicación preliminar sobre los hallazgos patológicos de histoplasmosis demostrada en 21 lesiones circunscritas y en 16 lesiones clínicamente activas Además, hubo otros tres casos dudosos en cada grupo, los que se pensó eran de histoplasmosis pero en los que no se encontró el parásito

En 24 especímenes más que se examinaron no se encontró el histoplasma Estos sirvieron como control porque se trataba principalmente de tuberculosis en los que se descubrieron bacilos ácido resistentes y en tres casos se encontró carcinoma bronquiogénico Se incluyen porque tienen gran similaridad clínica, radiológico y por otros hallazgos

Hubo cuatro casos clínicamente activos con bacilo de la tuberculosis y al mismo tiempo histoplasma capsulátum

Además, tres casos de sarcoidosis conocida así como muchos controles de otras enfermedades fueron teñidos y examinados pero no se encontraron los parásitos

Las series de casos fueron dos una incluyendo los aparentemente inactivos de la enfermedad como los llamados lesiones en forma de "moneda" y la otra, de clínicamente activos

Los hallazgos fueron como sigue Grupo 1 lesiones esféricas formadas centrífugamente, Grupo 2 infiltrados encapsulados, Grupo 3 lesiones caseosas nodulares parecidas a tubérculos caseosos de 1 a 15 mm de diametro y lesiones calcificadas y calcificadas osificadas, el Grupo 4 era de neumonitis crónica que se cree se divide en diferentes fases de edad de desarrollo desde la infiltración histiocítica y la neumonía fibrinosa temprana organizante con histiocitos hasta a granulomatosis tardía de la lesión que simula la sarcoidosis, el Grupo 5 era de las formas ulcerosas que se dividen en caseo-ulcerosas (etapa avanzada de la caseonodular y el tipo fibroide de lesiones que van desde la de paredes delgadas, quísticas, a las moderadamente engrosadas en la pared y a las cavidades con paredes fibrosas gruesas, el Grupo 6 era de bronquiectasia pura que no se puede distinguir en apariencia de cualquiera otra bronquiectasia pero que se encontró eran resultado de la infección por H capsulátum, el Grupo 7 del tipo pleural debida a la invasión de la pleura por el H capsulátum, el Grupo 8 fué una combinación de dos o más de los grupos anteriores

Al preparar el examen de este material se hizo un estudio agotando las posibilidades de muchos "artefactos" que pudieron quitar o identificar por colorantes especiales cuando fué factible

El mejor colorante para los cuerpos de esas levaduras fué el de Gomori metenamina plata (G M S) como se adaptó para la identificación de levadura por Grocott

De los 16 casos francamente activos e identificados, se cultivaron 14 y/o se inocularon en ratones pero sólo 7 fueron positivos

Los hallazgos fueron confirmados cuando fué posible por medio del polariscopio según lo recomiendan Potenza y Feo Aunque no es diagnóstico, muestra la presencia de una substancia polarizante que probablemente es un polisacárido

Se presenta una teoría la sobre la posible evolución de los parásitos en el cuerpo desde la celdilla fagocitada en los macrófagos hacia una forma semejante a esporas en el tejido fibroide y después un despertar de estas formas semejantes esporas (endosporas) hacia las celdillas de levaduras activas en un término que puede variar de meses a años y décadas

Se llevará a cabo un estudio ulterior de estas posibilidades y se espera poder entonces discutir esto más adelante

RESUME

Il s'agit d'une communication préliminaire sur la constatation vérifiée d'histoplasmose dans 21 lésions circonscrites et 16 lésions cliniquement actives Il y eut en outre trois cas douteux dans chaque groupe qu'on attribua à l'histoplasmose, mais dans lesquels aucun parasite typique ne put être trouvé

Dans 24 échantillons, on ne trouva pas d'histoplasmose Ils servirent de témoins, constitués par de la tuberculose, avec bacilles tuberculeux

et dans trois cas de carcinome bronchique Ils furent insérés dans cette étude a cause de l'étroite similitude des constatations cliniques et radiologiques avec l'histoplasmose

Dans quatre cas cliniquement évolutifs, se trouvaient associés des bacilles tuberculeux et l'histoplasmosis capsulatum

En outre, trois cas de sarcoidose connue ainsi que beaucoup d'autres soumis à investigations pour d'autres diagnostics, furent colorés et examinés, mais on ne put mettre en évidence aucun parasite

Il y eut deux groupes de cas, l'un comprenant les lésions apparemment inactives appelées "lésions en forme de pièce de monnaie" et l'autre consistant en affections cliniquement actives

Les constatations anatomo-pathologiques furent les suivantes — Groupe I lésions sphériques formées de manière centrifuge, — Groupe 2 infiltrats encapsulés, — Groupe 3 lésions caséeuses nodulaires, ressemblant à des tubercules caséeux de I à 15 millimètres de diamètre, et des lésions calcifées fibrocaséeuses, et ossifiées Le quatrième groupe comprenait une pneumonie chronique qui, pense-t-on, devait être divisée en plusieurs phases de développement, depuis l'infiltration histiocytique et une pneumonie fibrineuse s'organisant précocément avec histiocytes, jusqu'au dernier type granulomateux de lésion qui simule la sarcoidose Le groupe 5 était composé de types ulcératifs qui sont divisés en lésions caséo-ulcératives (stade avancé de type caséo-nodulaire) et le type de lésions fibreuses, qui s'étend de la cavité à parois minces, kystiques ou modérément épaisses, aux cavités à parois fibreuses épaisses Le groupe 6 comprenait un type bronchiectasique pur, qui ne put être distingué en apparence d'aucune autre bronchiectasie, mais qui se montra être du à l'histoplasmosis capsulatum Le groupe 7 était un type pleural consécutif à l'infection de la plèvre par l'histoplasmosis capsulatum, un huitième groupe fut un composé de deux ou plusieurs des autres types

En préparant les examens de ce matériel d'étude, une étude exhaustive fut faite sur les nombreux types d'artéfacts qui furent éliminés ou identifiés par des colorants spéciaux lorsque ce fut possible

Le colorant jugé le meilleur pour mettre en évidence la mycose fut l'argent méthénamine de Gomori (G M S) adapté par Grocott à cette recherche

Sur 16 cas actifs incontestablement positifs, 14 furent mis en cultures et/ou inoculés aux souris, mais 7 seulement se révélèrent positifs

Les constatations furent confirmées lorsque c'était possible par l'usage du polariscope, comme le recommandent Potenza et Feo S'il ne fait pas le diagnostic, il aide à montrer la présence d'une substance polarisante, probablement un polysaccharide

L'auteur propose une théorie sur l'évolution possible des parasites dans le corps humain, évoluant depuis les cellules phagocytées par les macrophages jusqu'à une forme sporulée quiescente dans le tissu fibreux, avec plus tard le réveil de ces spores (endospores) qui se transforment en levures actives après un temps variant de mois et d'années jusqu'à des décades

L'étude ultérieure de ces possibilités sera reprise dans un travail futur où une discussion plus étendue sera possible

ZUSAMMENFASSUNG

Es wurde ein vorläufiger Bericht zusammengestellt über die pathologischen Befunde von nachgewiesener Histoplasmose in 21 umschriebenen Herden und 16 klinisch aktiven Herden Zusätzlich ergaben sich 3 zweifelhafte Fälle in jeder Gruppe, bei denen eine Histoplasmose angenommen wurde, ohne dass man typische Parasiten hatte finden können

Es wurden 24 weitere Präparate untersucht, bei denen keine Histoplasmose gefunden wurde Diese dienten als brauchbare Kontrollfälle, weil es sich hauptsächlich um Tuberkulose handelte, bei denen säurefeste Bazillen gefunden wurden, und 3 Fälle von Bronchuskarzinom Sie wurden mit hinzu genommen in Anbetracht der grossen Ähnlichkeit der klinischen, röntgenologischen oder anderen Befunde mit der Histoplasmose

4 klinisch aktive Fälle lagen vor, die sowohl säurefeste Bazillen, als auch H capsulatum enthielten Ausserdem wurden 3 Fälle von nachgewiesenem Sarkoid ebenso wie viele Kontrollfälle mit anderen Krankheiten gefärbt und untersucht, aber Parasiten wurden nicht gefunden

Es lagen 2 Serien von Fällen vor, die eine umfasste scheinbar inaktive Erkrankungen mit sogenannten Rundherden, und die andere bestand aus klinisch aktiven Krankheitsfällen

Folgendes waren die pathologischen Befunde Gruppe I mit zentrifugal geformten sphärischen Herden, Gruppe II mit verkapselten Infiltraten, Gruppe III mit käsigen knötigen Herden, ähnlich wie käsige Tuberkeln im Durchmesser von 1—15 mm sowie fibrokaseose kalkhaltige und kalkig ossifizierte Herde, die IV Gruppe bestand aus chronischen Pneumonien, und es wurde für richtig gehalten, sie zu unterteilen in verschiedenen Phasen ihrer zeitlichen Entwicklung von der histiozytären Infiltration und frühzeitig sich organisierenden Pneumonie mit Histiozyten bis zu den späten granulomatösen Herdformen, die ein Sarkoid vortäuschen, Gruppe V war der ulzeröse Typ mit Unterteilung in käsig-geschwürige (ein weiter entwickeltes Stadium der käsig-knötigen) und den fibrösen Typ von Herden Letzterer reichte von dünnwandigen zystischen, über mässig dickwandige zu fibrös-dickwandige Kavernen Die VI Gruppe bestand nur aus Bronchiektasen, die im Aussehen nicht unterschieden werden können irgendwelchen anderen Bronchiaktasen, von denen sich aber heraus stellte, dass sie die Folge einer Infektion mit H capsulatum waren Gruppe VII war der pleuritische Typ, der die Folge der Invasion der Pleura mit H capsulatum ist Eine VIII Gruppe war eine Zusammensetzung von 2 oder mehreren der anderen

Bei der Vorbereitung zur Prüfung dieses Materials wurde eine erschöpfende Studie angestellt über viele Typen von Artefakten, sie wurden entfernt oder identifiziert mittels Spezialfärbung, so oft es ging

Als die beste Färbe zur Färbung von Sprossenpilzkörpern erwies sich die Gomori-Methenamin-Silber Färbe (G M S), die von Grocott als für die Identifizierung geeignet angegeben wurde

Von den 16 endgultig positiven aktiven Fallen wurden 14 kulturell verarbeitet und/oder an Mause verimpft, jedoch nur mit 7 positiven Ergebnissen

Die Befunde wurden, wo es moglich war, bestatigt durch die Verwendung des Polarisskops nach der Empfehlung von Potenza und Feo Wenn auch nicht von diagnostischem Wert, zeigt es doch die Anwesenheit einer polarisierenden Substanz, wahrscheinlich eines Polysaccharids

Eine Theorie wurde entworfen hinsichtlich der moglichen Entwicklung der Parasiten im Korper aus den phagozytierten Zellen in den Makrophagen zu einer ruhenden sporenartigen Form im Bindegewebe mit spaterer Reaktivierung dieser sporenartigen Formen (Endosporen) zu aktiven Sprossenpilz-Zellformen wahrend eines Zeitraumes, der schwankte zwischen Monaten, Jahren und Jahrzehnten

Eine weitere Ausarbeitung dieser Moglichkeiten wird in einer folgenden Arbeit ausgefuhrt werden, in der auch eine grossere Diskussion moglich ist

REFERENCES

1 Darling, S T "A Protozoon General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymph Nodes," *J A M A*, 46 1283, 1906

2 Schwarz, J, Baum and G L "The History of Histoplasmosis 1905-1956," *New England J Med*, 256 253-258, 1957

3 Furcolow, M L *Proceedings of the Conference on Histoplasmosis*, Public Health Monographs No 29, p 3, 1952

4 Darling, S T "Histoplasmosis Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America," *Arch Int Med*, 2 107, 1908

5 Meleney, H E *Problems in the Histological Diagnosis of Histoplasmosis* Proceedings of the Conference on Histoplasmosis 1952 Public Health Monographs No 39, p 14

6 Bauer, H "Mikroskopich-Chemischer Nachweis Von Glykogen und einigen anderen Polysacchariden," *Ztschr f Mikr Anat Forsch*, 33 143, 1933

7 Kligman, A M, Mescon H and De Lamater, S D "The Hotchkiss-McManus Stain for the Histopathologic Diagnosis of Fungus Disease," *Am J Clin Path*, 21 86, 1951

8 Gridley, M F "A Stain for Fungi in Tissue Sections," *Am J Clin Path*, 23 39, 1953

9 Gomori, G "A New Histochemical Test for Glycogen and Mucin," *Am J Clin Path Tech Bull*, 16 177, 1946

10 Grocott, R G "A Stain for Fungi in Tissue Sections and Smears," *Am J Clin Path*, 25 975, 1955

11 Schwarz, J *General Aspects of the Pathology of Histoplasmosis*, Proceedings of the Conference on Histoplasmosis 1952, Public Health Monographs No 39, p 12-13

12 Pinkerton, H E Idem p 17

13 Christie, A and Peterson, J C "Benign Histoplasmosis and Pulmonary Calcifications," *Am J Dis Child*, 72 460, 1946

14 Binford, C H "Histoplasmosis Tissue Reactors and Morphologic Variations of the Fungus," *Am J Clin Path*, 25 25, 1955

15 Straub, M and Schwarz, J "Healed Primary Complex in Histoplasmosis," *Am J Clin Path*, 25 727, 1955

16 McLauren, A, Beamer, P R and Tuttle, D M "Morphologic, Biochemical and Immunological Studies on Several Stains of Histoplasma Capsulatum," *Am J Path*, 27 751, 1951

17 Salvin, S B *Proceedings of Conference on Histoplasmosis* Public Health Monographs, 39 46, 1952

18 Potenza, L and Feo, M "Use of Polarized Light in Diagnosis of Mycotic Infections," *Am J Clin Path*, 26 91, 1956

Bronchial Photography with Simple Apparatus in Sanatoria

TAUNO PALVA, M D
Turku, Finland

Interest in bronchial photography centers mainly around two aims visual material is obtained for consultation and for teaching, and permanent records of clinically interesting cases are made for further reference and follow-up The pioneer work has been done in America by Holinger[1], in Europe Soulas[2] and the French school have contributed much to start this field In these large centers most of the recording is made with a film camera This gives the advantage of also observing the motion but increases the cost of the apparatus, so that it cannot be acquired by smaller institutions

For purposes of case studies in a sanatorium it is sufficient to be able to make still pictures of the observed lesions in the bronchial tree This enables the whole staff to see the extent and location of the bronchial changes, which otherwise are only seen by the bronchologist through the tube and telescopes

Two recent techniques of bronchial photography have been described, both of which are based on the same idea the illumination is led via a quartz rod into the tip of the bronchoscope The apparatus by Dubois de Montrenayd[3] employs a 6 V proximal auto lamp as a source of continuous light, which makes also bronchial films possible The apparatus is now becoming commercially available, but its total price would still be a considerable burden on the economy of smaller clinics

Another apparatus, commercially available for a short time (manufactured by the Storz Company), employs an electronic flash as a proximal light source Because of this, only momentary pictures can be taken The price of the apparatus is in reasonable limits and nearly all institutions interested in bronchial photography are in a position to purchase it Experience with this equipment will be reported here

Apparatus and Technique

Bronchoscope The tube is of elliptical diameter with 8x10 mm outsurface diameters The distal end of the tube is somewhat broader than usual, and it is often necessary to turn the tube 90 degrees to the side when passing the vocal cords Otherwise the broad tip may be difficult to introduce without traumatizing the epithelium of the cords

Telescopes These can be obtained with straight angle, 45 degrees, and straightforward vision Each telescope accommodates a quartz rod running parallel to the viewing tube proper It is necessary to give oxygen through the bronchoscope during photography as the telescopes occupy most of the tube space A flow of 8 to 10 liters/min is enough to allow the patient sufficient oxygen when the pictures are made

---

[1]From the Satakunta Sanatorium

The greatest trouble in securing good pictures is to keep the moisture out of the lenses I have found it best to keep the tips of the telescopes in a folded electrical heat-bag before they are used for photography The temperature of the bag is not too hot for the bronchi as the telescopes do not contact the mucous membranes and there is enough time for making bright pictures before cooling causes blurring of the lenses with moisture

Illumination An electrical flash bulb is housed in each telescope and receives the current from a transformer, the length of the flash is less than 1/50 sec A picture can be taken every 2 or 3 seconds In the meantime the transformer is not ready to give the bulb another current stroke

Camera A Robot Star camera with a well fitting tip for the proximal end of the telescope is used The automatic film shifting mechanism enables the whole series of pictures in one patient to be taken successively without rewinding the mechanism The camera has a separate eye piece for the examiner who is able to see all the time while pictures are being taken This contributes greatly to the success of the pictures since the exact location of the telescope and an unblurred view can be maintained

The brightness provided by the flash is sufficient for Ectachrom film, but also black and white film can be used if prints are desired The prints can be added to the patient's records, enlarged from the original 1 cm diameter negative The color slides can be stored with detailed notes of the pictures and examined with a projector

Dubois de Montrenayd[3] reports that in their clinic a film strip is made of the bronchi at every bronchoscopy regardless of whether the findings are normal or pathological While realizing that this practice would be ideal for any follow-up study, I have made still pictures of the findings only if there have been evident gross changes in the bronchi Generally I examine the bronchial tree first with ordinary telescopes and at this stage determine the areas to be photographed The straight-vision photographic telescope is always used first because it employs the distal light of the bronchoscope itself For the upper lobes, the straight angle photographic telescope is introduced The structure of the apparatus necessitates switching off the distal bronchoscope light in order to furnish the telescope with illumination After the upper lobe pictures are taken, the telescope is withdrawn and the bronchoscope light reconnected

After the desired photographs have been taken the bronchographic procedure, employed routinely in combination with bronchoscopy, is made by a method previously described[4] The tube is withdrawn, the patient is wheeled to the roentgen department and bronchograms are made

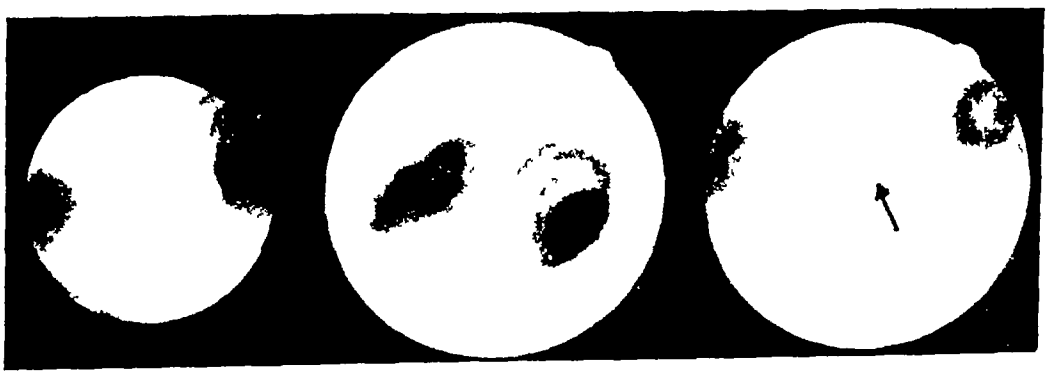
Results and Comment

It has been pointed out earlier[4,5] that to limit the examination of the bronchial tree only to the major bronchi, as is done in bronchoscopy, leads to an incomplete and sometimes erroneous conclusion regarding the condition of the bronchi There are, of course, numerous cases where the pathological changes are localized in the area visualized in bronchoscopy, but there are also many others in which the changes seen in bronchoscopy

are only minor reflections of much greater pathology beyond vision For a more definite judgment of the therapeutic measures needed for each individual patient, it is therefore often necessary to map the medium-sized and smaller bronchi with contrast medium The typical photographic findings are therefore in some cases discussed together with the information obtained from the bronchograms

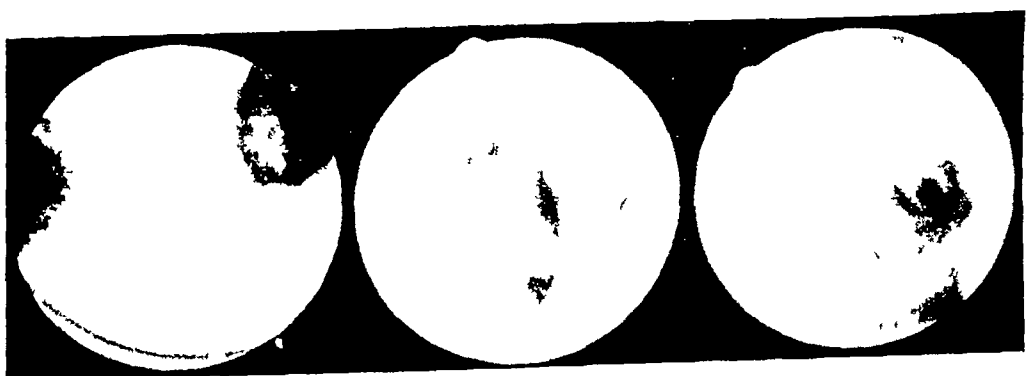
The carina is the first landmark whose appearance often shows deviations from the normal In figure 1A a normal carina is seen with thin mucous membranes and clearly defined intercartilaginous depressions In figure 1B the carina is distorted owing to a scirrhous right upper lobe process, on the right in figure 1 there is a flattened carina with an open fistula (arrow) leading to a tuberculous glandular involvement under the carina

Carcinoma of the bronchus (Fig 2), if readily visualized, generally does not need an additional bronchogram In our experience photographs of the involved area are of great help as the extent of the lesion can be exactly seen and studied at leisure by the whole staff in consultation with the thoracic surgeon In Fig 2 the epidermoid carcinoma involves the carina (2A), occludes a large part of the right main bronchus (2B), and extends on the lateral wall beyond the orifice of the middle lobe bronchus (2C)



A B C

FIGURE 1 A Normal carina B Distorted carina C Carina with an open fistula



A B C

FIGURE 2 Bronchial carcinoma A Infiltration of carina B Carcinomatous growth in the whole right main bronchus C Infiltration of the lateral wall at the level of the middle lobe orifice

Bronchiectasis is not often definitely diagnosed bronchoscopically, especially if the patient has already expectorated the mucus out of the bronchi *Figure 3 depicts a case of this kind where the right side shows nearly normal middle and lower lobe bronchi* (Figs 3A and 3B) The bronchogram, however, shows clear cylindrical and saccular bronchiectasis both in the middle lobe and in the basal lower lobe segments (Fig 3C)

On the same patient the diagnosis of bronchiectasis could be made definitely, even before the bronchogram, from the abundance of the secretions on the left side Figures 4A and 4B show views before and after suction at the level of the three basal segmental bronchi The bronchogram discloses that all three branches of the left lower lobe are involved *with saccular bronchiectasis (Fig 4G)*

Tuberculous changes in the bronchi can be seen in Figures 5 to 7 Pure inflammatory tuberculous processes without stenoses or granulations are best seen in the original ectachromes as the conversion into black and white fails to show most of the details of the epithelial surface Figure 5A shows a process in the right upper lobe the mucous membrane is thick and edematous The narrow orifice of the posterior segment is clearly visible but the others are covered with yellow pus extruding from the narrow apical opening The bronchogram of this patient (Fig 5B) shows a rather

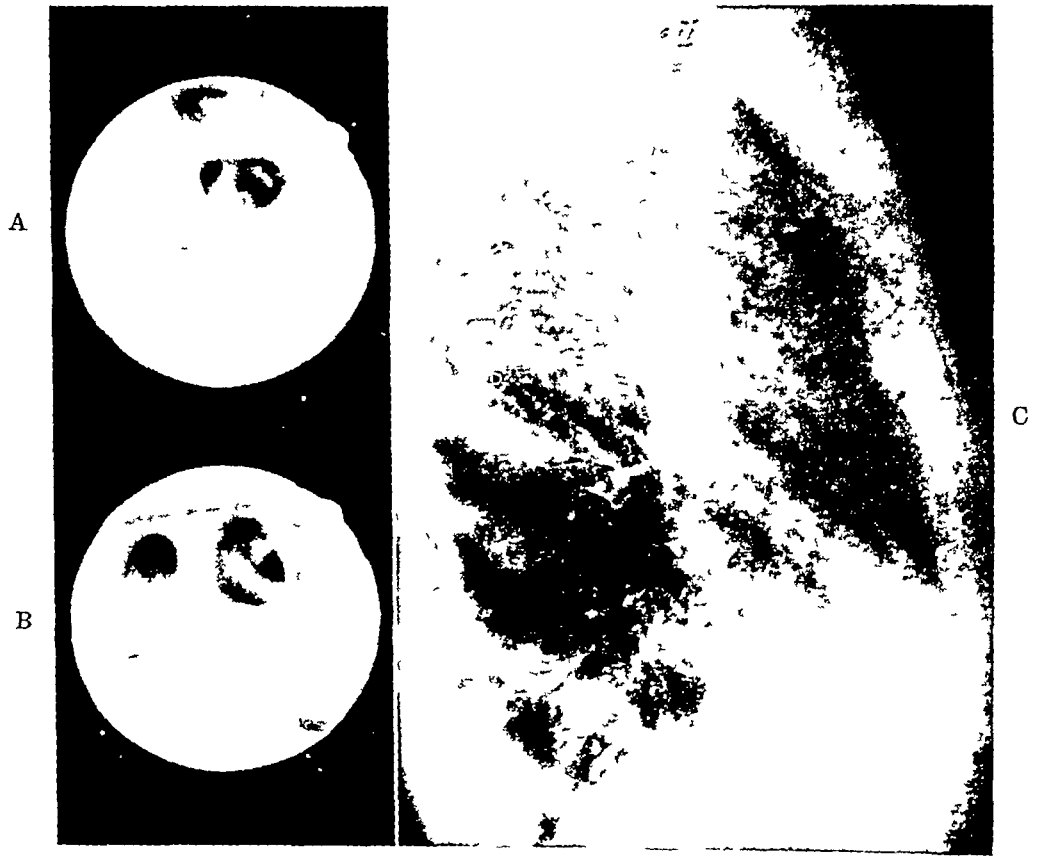


FIGURE 3 Bronchiectasis A Middle lobe and entrance to the lower lobe B Lower lobe orifices C Lateral projection bronchogram with bronchiectasis in the middle lobe and basal lower lobe segments

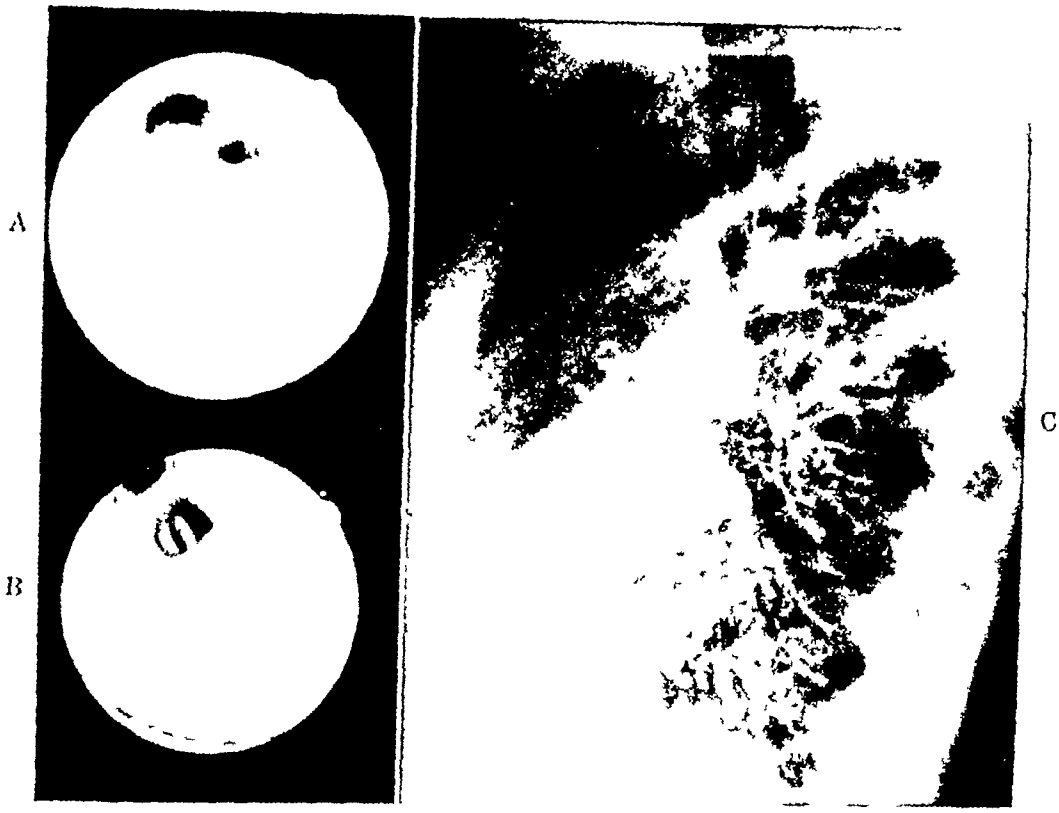


FIGURE 4 Bronchiectasis A Left lower lobe before suction B The three basal segmental orifices after suction C Lateral projection bronchogram with bronchiectasis in the basal lower lobe segments

FIGURE 5 Tuberculous endobronchitis and bronchiectasis A Active inflammatory process in the right upper lobe B A-P projection bronchogram with bronchiectasis in the apical and posterior segmental bronchi.

narrow branching for the three segmental bronchi of which especially the apical and posterior division are ectatic

Figure 6 shows a case with old, inactive stenosis at the level of the right middle lobe bronchus Only a narrow rim of the middle lobe bronchus is seen while a tense, fibrous scar surrounds the medial part of the middle

FIGURE 6 Inactive tuberculous stricture A Entrance to the right lower lobe, above it a narrow orifice to the middle lobe Healed scar tissue surrounds both orifices at the medial wall B Lateral projection bronchogram with narrowed lumina at the junction of the middle and lower lobe bronchi

FIGURE 7 Tuberculous endobronchitis A Inactive, right upper lobe process with narrow orifices and thick intersegmental septa B Healed scar in the medial wall of the left lower lobe bronchus C Open fistula at the level of the mediobasal segment of the right lower lobe bronchus D Occlusion of right lower lobe bronchus with tuberculous granulomatous lesion

and lower lobe entrance (Fig 6A) In the bronchogram (Fig 6B) this scanty branching is evident However, it is worth noticing that middle lobe bronchi fill well in spite of the deformed anatomy

Further tuberculous changes are shown in Figure 7 Figure 7A shows a right upper lobe orifice with very thick intersegmental septa but with non-active mucous membrane In Fig 7B an old scar, resulting from a healed fistular process, is seen in front of the basal segments of the lower lobe bronchus (arrows) Figure 7C shows an open fistula (arrow) in the right lower lobe bronchus as the level of the mediobasal segment Finally, in Fig 7D, an active, stenosing, granulomatous occlusion of the lower lobe bronchus is seen in the right bronchus at the level of the middle lobe orifice

Bronchial photography gives in many cases valuable data for case conferences in a sanatorium and makes the pathological bronchial changes, described by the bronchologist, clearer and more meaningful to the phthisiologist Together with the bronchogram, and with analyses of the bronchial secretions,[6] bronchial photography helps to clarify the condition of the bronchial tree

SUMMARY

Experience with bronchial photography in a sanatorium is reported The apparatus is simple and not expensive, only still pictures can be made Typical gross changes in the bronchi are described Photographs of the lesions are valuable in staff conferences, consultations, follow-up studies, and in teaching

RESUMEN

Se informa de la experiencia con la fotografía bronquial en un sanatorio El aparato es sencillo y no costoso, sólo se toman vistas fijas Se describen las alteraciones gruesas típicas en los bronquios Estas fotografías son valiosas para las conferencias del personal medico, consultas, seguimiento de enfermos y para la enseñanza

ZUSAMMENFASSUNG

Bericht uber Erfahrungen mit bronchialer Fotografie in einem Sanatorium Die Apparatur ist einfach und nicht kostspielig, es konnen nur unbewegliche Bilder gemacht werden Typische makroskopische Veranderungen in den Bronchien werden beschrieben Fotografien der Herdbildungen sind von Wert bei Konsilien, Konsultationen, Verlaufsbeobachtungen und fur den Unterricht

REFERENCES

1 Holinger, P H "Photography in Otorhinolaryngology and Bronchoesophagology" In "Otolaryngology" ed by Coates, Schenck and Miller, Prior Co, Hagerstown, 1956
2 Soulas, A "Bronchoscopie, Bronchographie, Cinematographie en Bronchologie," *Ann Oto-Laryng*, (Paris), 72 668, 1955
3 Dubois De Montrenayd, J-M, Edwards, R J and Gladu, A-J "A New Method of Bronchoscopy with Cinematography and Photography," *Laryngoscope*, 66 637, 1956
4 Palva, T, Elo, R and Saloheimo, M "The Role of Bronchoscopic Studies in Pulmonary Tuberculosis," *Dis Chest*, 32 56, 1957
5 Palva, T, Elo, R and Saloheimo, M "Bronchoscopy in Pulmonary Tuberculosis," *Acta Tub Scand*, 33 241, 1957
6 Gronroos, J A, Palva, T and Saloheimo, M "Bronchoscopic Observations in Pulmonary Tuberculosis With Special Reference to Cytologic and Bacterial Findings," *Acta Tub Scand*, 32 163, 1956

Abeyant Tuberculosis*

ABRAHAM GELPERIN, M D **

Kansas City, Missouri

Abeyant tuberculosis is a state of armed neutrality between the host, man and the tubercle bacillus In particular, it is a prognosticative as well as descriptive label for those individuals with evidence of past tuberculous infection, and no evident clinical disease It describes the group that produces much of the communities' active, infectious cases of tuberculosis

The importance of abeyant tuberculosis became manifest during 1952-53 in the course of an evaluation of the tuberculosis control program in Polk County, Iowa [1] A study of the median ages in relation to the stage of reported disease showed minimal, about 30 years, moderately advanced, about 45 years, and far advanced, about 55 years Among those who sought medical attention because of symptoms, there were slightly more women than men in the moderately advanced group, while among those with advanced disease, there were almost four times as many men as women

It was found that 52 (63 per cent) of the 83 new cases of tuberculosis reported during the two year period came to the doctor because of symptoms of actual illness In addition, a serious time lag between first suspicion of illness to final diagnoses became evident Although 22 (27 per cent) were diagnosed within three months, the median time between onset of symptoms and diagnoses was over six months Of the total group, 19 (23 per cent) had a delay of more than one year The inescapable conclusion was that in a low incidence area, there was need for a re-evaluation of case finding and educational methods and techniques based upon the facts as ascertained as well as the changing character of the disease itself

First, it must be acknowledged that active tuberculous disease is frequently difficult to diagnose, that physicians hesitate to treat anyone upon initial suggestive physical and/or x-ray evidence alone in the absence of positive laboratory findings, and rightly so

Second, the great majority of clinically active tuberculous disease results from a reciudescence of previously abeyant infection We must remember that the morbid picture of only a few decades ago when large numbers of young persons developed tuberculous pneumonias or extensive, rapidly progressive disease was the host-parasite relationship in the environmental and medical care setting of that period Now, the problem

---

*Presented at the Annual Meeting, Iowa Tuberculosis and Health Association and Iowa Trudeau Society Meeting, Des Moines, Iowa, April 10, 1957

**Director of Health and Hospitals, Kansas City, Missouri

focuses primarily upon men over 40 Clinically active tuberculosis is no longer predominantly a disease of youth

Third, our communities have been lulled by the huzzas of the professions over the dramatic, continuing decline in the tuberculosis mortality rates, in spite of the distressingly slower decline in morbidity rates

Fourth, x-ray screening surveys do not detect the individuals who have been infected, and do not present evidence of active pulmonary disease These are individuals who were temporarily victorious in their first encounter with tubercle bacilli

These overlooked individuals have abeyant tuberculosis They constitute the group of people that in the past have been given to believe that they had healed themselves When this belief is coupled with the fact that people's attitudes toward both tuberculosis and detection programs are still frequently colored by fear and/or misunderstanding, the usual x-ray survey programs are foredestined to only partial fulfillment of function

A recent inquiry in three high incidence areas as to why people obtain x-ray films showed that those who believed they might get tuberculosis, those who do not rely solely on symptoms as a stimulus for seeking a chest x-ray film, and those who see benefits to themselves in early detection are likely to obtain x-ray films voluntarily regardless of economic status, sex, or age (2) What became evident however, was that what people do or do not do is not a function of information Action results from a real belief and a conviction that such information applies to them personally and that it is important to them as individuals Education, or information in itself is neither motivation nor action

All these factors are the basis of a pilot study initiated in Polk County during 1956, a program to bring under Health Department surveillance those individuals with evidence of past tuberculosis infection, and no clinical disease This was centered for Polk County in the local health department, and co-ordinated with the State and County Tuberculosis & Health Associations, our health professions, schools, multitude of interested community groups and agencies, as well as U S Public Health Service, and the State Health Department It is supported as a research project by the Iowa Tuberculosis and Health Association

A companion follow-up file to the usual tuberculosis registry was created for those with abeyant tuberculosis The card, specially designed for this investigation is in a section of the tuberculosis case registry file The abeyant file will be fed from several sources, the tuberculin testing programs in schools, contacts to cases of active disease, private physicians, as well as the county-wide miniature x-ray filming service Those with suggestive x-ray evidence of past tuberculosis infection will be tuberculin tested for verification The importance of the tuberculin test as either a necessary adjunct to x-ray film surveys or as a screening procedure is manifest

Children with positive tuberculin reactions will be placed in the Abeyant File upon reaching the age of 15, as well as act as the reason for testing their adult contacts With the recent extension of the local x-ray film

program to the community groups with the highest morbidity, jail, transient and elderly populations, it will be possible to separate out those individuals who must be followed and from whom we can expect the active tuberculosis of the tomorrow It is of interest that this program during 1956 produced two cases of active tuberculosis from 88 transients x rayed, three cases in 405 persons in our city and county jails, and none in the 865 elderly individuals from Golden Age Clubs and nursing homes The first two groups produced one active case of tuberculous disease per 100 films In addition, there were 26 individuals with findings suspect of tuberculosis, the old age group produced but seven such persons It would have been these individuals who would spread the disease to their families and community, unknowingly, and for many months, if not uncovered and kept under surveillance

Since its initiation, the file is accumulating slowly It was planned to start cautiously The committee responsible for this program has clarified the study and its import to date by concluding

1 Only those with a positive tuberculin reaction will be in the Abeyant File, irrespective of original method of referral
2 Those groups with the highest incidence of disease require added Health Department and Tuberculosis Associations' efforts
3 Education material, pertinent to the goal of the program will be sent to those placed in the abeyant file along with the predetermined periodic reminders to have a chest x-ray film
4 An indication of intention will be sent whereby public health nurses can concentrate on those who do not intend to follow through on their own accord
5 A routine of notification will permit follow-up of those who will not have availed themselves of x-ray services
6 An acknowledgment that the project has several values, case findings, case holding, health education and research, with an opportunity to evaluate each facet

Of special importance is the opportunity to study the methods and techniques necessary and peculiar to motivating people with Abeyant Tuberculosis A person must know what to do, when to do it and how to do it before he can take action But merely knowing these things is insufficient in itself to elicit the action to which they relate There must be motivation The least desirable is passive acceptance of easily available x-ray screening services brought to people with the added prompting through exhortation and veiled dire prophecies The ultimate is for informed people to do that for themselves which they know they should do for themselves

It is hoped that with careful and meticulous study and evaluation it can be determined how best to progress toward the goal of developing the individual's sense of responsibility for his own health as well as fulfill our responsibilities in tuberculosis control of uncovering as well as preventing tuberculous disease and its spread through our community

SUMMARY

A pilot study was initiated to follow by means of periodic reminders as well as follow-up visits by nurses of the Des Moines-Polk County Health Departments of all individuals with abeyant tuberculosis (tuberculin reaction but no evident clinical disease) brought to the attention of the health department from x-ray or tuberculin surveys

This group with evidence of past tuberculous infection is considered to produce much of the community's active tuberculosis Re-evaluation in the county had emphasized this fact

The preliminary study will permit evaluation of case finding, case holding, and health education as it pertains to those previously ignored individuals in whom there is a state of armed neutrality between the host and tubercle bacillus

RESUMEN

Se inicio un estudio piloto para observar a los individuos infección tuberculosa (con reacción tuberculinica, pero sin evidencia clinica), se ha emprendido por medio de recordatorios periódicos así como por visitas de observación por enfermeras del Departamento de Salubridad del Condado de Polk en Desmoines Estos infectados fueron descubiertos por el departamento de Salubridad por los rayos á o por investigaciones tuberculínicas.

Este grupo con evidencia de infección tuberculosa anterior se considera que produce mucha de la tuberculosis activa en la comunidad

La revalorización en el condado ha destacado este hecho

El estudio preliminar permitirá estimar la busqueda de casos, el control de los casos, y la educacion higiénica como corresponde a estos individuos antes ignorados en quienes hay un estado de neutralidad armada entre el huésped y el bacilo

RESUME

Une étude-pilote fut entreprise pour suivre au moyen de rappels périodiques aussi bien que de visites systématiques par des infirmières des Services de Santé du "Des Moines-Polk County Health Departments" tous les individus ayant une tuberculose stabilisée (réaction tuberculinique positive, mais sans atteinte clinique évidente) signalée à l'attention du service de santé par des contrôles radiologiques ou tuberculiniques

Ce groupe de malades, porteurs d'une infection tuberculeuse ancienne évidente, est considéré comme produisant le grand nombre des tuberculoses actives de la collectivité Une nouvelle estimation dans la région a mis ce fait en évidence

L'étude préliminaire permettra d'évaluer l'importance du dépistage, du traitement, et de l'éducation sanitaire, puisqu'elle s'adresse à des individus antérieurement ignorés chez lesquels il existe un état de neutralité armée entre l'hôte et le bacille tuberculeux

ZUSAMMENFASSUNG

Eine wegweisende Untersuchung wurde begonnen, um sowohl mit Hilfe periodischer Erinnerungsschreiben als auch mit Verlaufsbeobachtungsbesuchen von Pflegerinnen der Gesundheitsamter des Kreises Des Moines-Polk das Schicksal aller Individuen zu verfolgen mit unentschiedener Tuberkulose (positiver Tuberkulinreaktion, aber keine klinisch augenscheinliche Erkrankung), wie sie zur Kenntnis des Gesundheitsamtes durch Rontgen- oder Tuberkulin-Reihenuntersuchungen gelangt war Von diesem Personenkreis mit Anhaltspunkten einer vorausgegangenen tuberkulosen Infektion wird angenommen, dass er viel beitragt zu den kommunalen aktiven Tuberkulosen Eine Zeitberechnung im Kreis hat diese Tatsache unterstrichen

Die vorlaufige Untersuchung wird eine abschatzung der Fallsuche, des Fallbestandes und der Gesundheitserziehung ermoglichen, wie sie solchen zuvor ubersehenen Personen zukommt, bei denen ein Zustand bewaffneter Neutralitat besteht zwischen dem Wirt und dem Tuberkelbazillus

REFERENCES

1 Gelperin, A, Galinsky, L J and Iskrant, A P "Appraisal of Tuberculosis Case Finding," *Pub H Rep*, 70 761, 1955

2 Hochbaum, G M "Why People Seek Diagnostic X-rays," *Pub H Rep*, 71 377, 1956

Bronchoscopic Criteria for the Diagnosis of Tuberculous Lymph Node Perforation into the Bronchial Tree of the Adult

A Critical Analysis of 700 Cases

J ADLER, M D , Z HERMAN, M D and H SPITZ, M D *
Beer Yaacov, Israel

Perforation of caseous lymph nodes into the bronchial tree is of relatively frequent occurrence in the course of tuberculosis in children The importance of this complication in the pathogenesis of the disease as well as in certain clinical and roentgenological findings is well understood by clinicians and pathologists It has also been known for many years that in elderly people anthracotic or caseous lymph nodes may occasionally break through into bronchi or into mediastinal structures, sometimes causing serious clinical manifestations With the introduction of large-scale bronchoscopy, lymph node perforations were also observed in adolescents and young adults suffering from pulmonary tuberculosis especially in the primary or post-primary phase of the disease,[1] but according to most observers active tuberculous processes of pulmonary lymph nodes are of no great practical importance in the adult type of pulmonary tuberculosis

Pathologists like Schwartz[2,3,4] and Uhlinger[5] oppose this generally accepted view On careful systematic investigations on autopsy material of more than 700 cases Schwartz observed in a large proportion of cases lymph node penetrations into the airways of adults suffering from pulmonary tuberculosis in all stages In his opinion, periodic re-activation and perforation of caseous pulmonary lymph nodes are responsible in most cases for endogenous re-infection and for the spread of the process in chronic pulmonary tuberculosis of the adult

Some recent bronchoscopic observations seem to support the theory of Schwartz In a number of publications from various clinics, bronchoscopists recorded perforations or residues of perforations with great frequency in adult patients Lévi-Valensi, Zaffran and Morena[6] describe 25 bronchial fistulae in Algerian patients 18 to 61 years of age Vaksvik,[7] on bronchoscopic examination of 1003 adult patients in Norway, found 134 cases with perforations or residues of perforations Iselin and Suter[8] and Meng[9] report similar numbers from Switzerland 131 perforations or scars in 1370 consecutive bronchoscopies Tricoire[10] in France observed 16 cases of lymph node perforation in adults and quoted a publication of Chatonnier and Zaffran[11] who found 37 fistulae in 120 adult patients Most recently,

* This article is based on our experience in the Department of Medicine, Surgery and Pathology, in the Malben Beer Yaacov Hospital for Chest Diseases, services of the American Joint Distribution Committee in Israel, which receives its budget from the United Jewish Appeal

Poppel c s [12] lepoi ted theii experiences in 1257 patients, 950 of whom suffered from pulmonary tuberculosis In 117 cases they found perfoi a-tions of lymph nodes oi bi onchial fistulae (109 in the tuberculous gi oup and eight in the non-tuberculous group)

The bi onchial findings described by vaiious authors may be grouped in pathognomonic and suggestive signs Pathognomonic signs of lymph node perfoi ation are bi oad iiiegulai funnel-shaped openings in the bi onchial wall, sui i ounded by, and pai tially filled with coarse gi anulation tissue In the fistulous ti acts caseous oi anthracotic material fi om the lymph nodes is visible Another characteristic picture is a fui uncle-like elevation of the mucosa with central umbilication In most cases, it is possible to expel by pi essure with the bi onchoscope some pui ulent mate i ial which usually contains tubercle bacilli On repeated bronchoscopies one can obsei ve that healing takes place by scai formation

As suggestive signs of lymph node perforation other bi onchoscopic pic-tures were described, e g round cii cumsci ibed openings in the mucosa, small ducts or as punched-out holes The diameter of these mucosal holes varies from pin-point size to 2 to 3 mm Frequently, the lumen widens during inspii ation The mucosa covei ing the holes is usually of noi mal appeai ance but at times may show signs of inflammation Not infi equent-ly mucous and even purulent secretion is observed and, in i are cases, smooth ti anslucent granulation tissue is found in the wall oi in the depth of the holes The French authoi s emphasize that the appeai ance of these open-ings does not change on i epeated bronchoscopic examinations

Indirect signs of former lymph node penetiation are described as muco-sal scai s—especially funnel-shaped or stai like retractions—humps or cal-lous prominencies, local discoloi ation of the mucosa or isolated patches of anthracotic pigmentation According to many authors, these findings make a diagnosis of a formei perforation likely, particularly if they appear in combination with cei tain clinical symptoms and i oentgenologic patterns Vaksvik is of the opinion that most cases of bi onchostenosis, ulcei ation or local pi olifei ation of gi anulation tissue are caused by pei foi ation of tuber-culous lymph nodes

Analysis of Oui Matei ial

In an attempt to i e-examine the theoi y of Schwartz and to i e-evaluate the bi onchoscopic findings of the above mentioned authoi s we made a sui-vey of 700 consecutive patients who had undei gone bi onchoscopic examina-tions dui ing the yeai s 1951-1954

At the Beer Yaacov Chest Hospital bi onchoscopic examinations are per-formed on evei y patient in whom clinical symptoms or i oentgenologic signs point to an involvement of the lymph nodes or of the bi onchi and, further-more, in every case that requires decision about possible opei ative interven-tion At evei y examination, the bi onchial ti ee including the orifices of the segmental bi onchi is carefully inspected with telescopes

Table I gives a summary of the most impoi tant lesions found We adopted the terminology of Vaksvik in oi der to be able to compare oui findings with

TABLE I

Bronchoscopic findings at	Glittre San 1946 - 1952		Beer Yaacov Hospital 1951 - 1954	
Number of patients	1,003		700	
Number of bronchoscopies	1,262		916	
Definite lymph node perforation	20	(2%)		
Suspected lymph node perforation			7	(8%)
Mucosal holes	81	(8%)	49	
Mucosal scars	33		8	
Stenosis	53		41	
Granulations	23		8	
Ulcerations	9		8	
"Cushions"	12		1	

those at Glittre Sanatorium The above table shows that we also found pathological changes in the bronchial wall in a great number of our patients For reasons which will be discussed later we do not accept many of the so-called indirect signs, described by other authors as characteristic for lymph node perforation and cases with such findings are not included in our analysis We selected 64 cases for further study, 8 of whom showed star-shaped or funnel-shaped retractions and 56 presented holes in the bronchial mucosa

With the exception of one boy of 16 all these 64 patients were adults, 18-57 years of age, the sex distribution was about equal All were recent immigrants, more than one half of them from Europe, while the others hailed from Arabian countries or from North Africa

Table II shows the number of bronchoscopies performed on individual patients In half of our cases more than one examination was made The time of observation was longer than six months in about one fourth of the cases Especially, when perforations were suspected repeated bronchoscopies were performed up to several years following the initial examination

TABLE II
NUMBER OF BRONCHOSCOPIES IN PATIENTS WITH SUSPECTED PERFORATIONS, MUCOSAL HOLES OR SCARS

No. of examinations	1x	2x	3x	4x	5x	6x	Total
No. of patients	32	19	7	1	4	1	64
No. of bronchoscopies	32	38	21	4	20	6	121

Interval between bronchoscopic observations	Mucosal Holes Mucosal Scars	Suspected Perforations
3 - 6 months	16	1
7 - 12 months	5	2
13 - 24 months	3	2
25 - 36 months	1	2

In the eight cases with distinct mucosal scars, we compared the bronchoscopic findings with the tomographic pictures All of them suffered from chronic phthisic form of tuberculosis and the mucosal scars were situated at the orifice of the bronchus leading to the main lesion In five cases, a calcified lymph node was found in close contact with the bronchial wall at the site of the scar, and in five the roentgenologic appearance was typical for obstructive or peribronchial lesions

As mucosal holes we considered circumscribed openings in the mucosa or small ducts from pin-head size to a diameter of 2 to 3 mm In more than one half of our cases only a single lesion was observed, in one third there were two holes, usually in the same bronchus In other patients we found a varying number of pathologic openings in different places, in two cases more than 10 holes were seen In a total of 49 patients 98 holes were encountered As may be seen in Figure 1a, the sites of predilection were the orifices of the right and left upper lobe bronchi, especially the anterior and lower walls, and to a lesser extent, the medial walls of the right and left main bronchi just beneath the carina The mucosa covering the holes appeared normal in most of our cases Frequently we observed inspiratory widening of the openings In seven patients the mucosa was reddened and swollen, whereas the surrounding bronchial mucosa was generally unaltered Mucous secretion was noted 14 times and minimal purulent secretion was found four times oozing from the openings In none of the cases was it possible to obtain sufficient material for a bacteriological examination In five we saw smooth translucent grayish-red granulations at the bottom of the holes Our observations correspond to those of other authors concerning number, localization and appearance

We do not think that these findings by themselves are sufficient to make a diagnosis of lymph node perforation We agree with Vaksvik that there are all sorts of transitional forms between active perforation, fistulous tracts and other pathologic openings in the bronchial tree

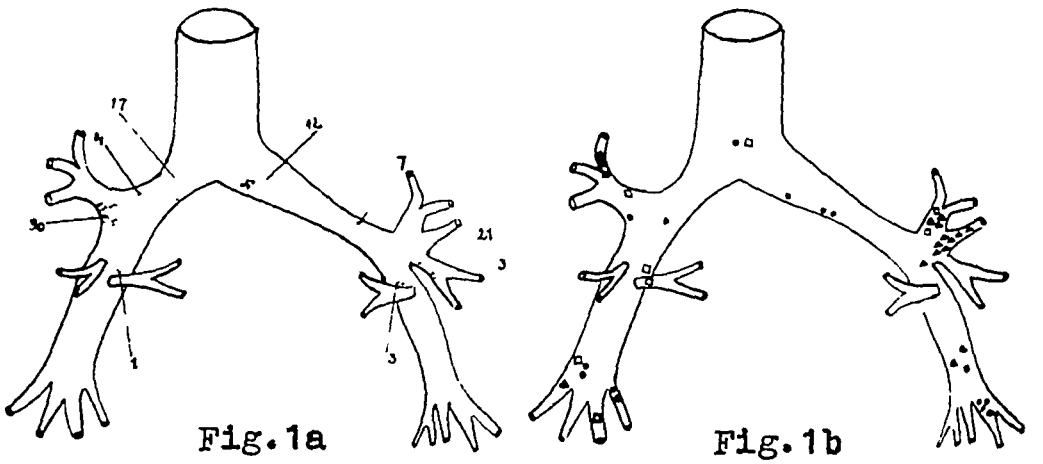


Figure 1a Distribution of 98 mucosal holes in 49 cases —*Figure 1b* Localization of holes (°), crypts (Δ), and patches of anthracosis (□) in 15 post-mortem specimens of bronchial tree

In the presence of larger openings the possibility of supernumerary or aberrant bronchi must be considered Bronchographic and tomographic examination can classify the nature of such findings The small holes, however, that were noted by us and by many authors quoted above* may represent fistulous tracts or pathologically enlarged ducts of the mucous glands

The acini of the mucous glands are situated deep below the bronchial mucosa A relatively long and narrow duct traverses the different layers of the bronchial wall in an oblique direction and widens before entering into the bronchial lumen Under normal conditions the small openings cannot be visualized Inflammatory processes involving the mucous glands or foreign material penetrating into the lumina of the ducts may cause abnormal dilatation Inflammatory changes at the narrow neck of the ducts may cause local obstruction followed by cystic dilatation of the glands, accumulation of purulent secretion in these sacs and finally perforation into the bronchial lumen Mechanical factors such as chronic cough possibly play also a part in the pathogenesis of these lesions

It is possible to demonstrate the dilated ducts or cysts on bronchographic examination They appear as small diverticuli or as isolated droplets When there are multiple cysts the bronchial wall appears serrated or irregular Huizinga[11] and after him other authors described the typical roentgenologic appearance especially in patients suffering from bronchitis or from bronchial asthma Figure 2 shows the bronchographic picture of glandular cysts in one of our patients, in whom we found more than 10 mucosal holes on bronchoscopic examination

Dupriez and Mampuys[14] studied the topography of the mucosal glands and the occurrence of dilated glandular ducts by means of bronchial casts

*Compare e g, the illustrations in the paper by Levi Valensi c s Rev de la Tubere, 15 410, 1951 pp 412-413

FIGURE 2 Bronchographic picture of mucosal holes

and of special preparations of the bronchial mucosa They found the pathologic changes most frequently in the larger bronchi around the bifurcations The authors compared their anatomic findings with the bronchoscopic appearance of mucosal holes and they stress that in most cases differentiation between glandular ducts and small fistulous tracts from bronchial lymph node perforations is impossible on bronchoscopic observation alone They believe that, not realizing these facts, many clinicians report too high a percentage of perforations

In our material none of the cases with mucosal holes, seen at bronchoscopy were available for anatomic study There was no death among the patients examined and in cases that underwent lobectomy or segmentectomy the holes, which had been visualized were situated always proximally to the surgical plane of resection

We, therefore, had to look for other comparable material and examined the tracheobronchial trees from individuals who died from various diseases The trachea, bronchi and both lungs were removed *in toto* from the body and the same examiner who had done the bronchoscopic examinations *in vivo* introduced the bronchoscope into these preparations and searched for holes However, none was found The trachea and the bronchi were, then, opened posteriorly by cutting them longitudinally with scissors and a thorough search for holes was made with the magnifying lens by both the bronchoscopist and the pathologist In this manner, a number of such lesions were discovered in spite of the negative findings on previous bronchoscopic examination by the lack of respiratory movements and dilatation so that the tiny holes remained collapsed and were further reduced in

FIGURE 3 Flask-shaped duct with fibrosis and lymphocytic infiltration Atrophy and cystic dilatation of bronchial glands

size by the postmortem contraction of the bronchial muscles The lesions were found lying singly or in groups at a location corresponding closely to that of the bronchial holes seen *in vivo* (Fig 1b)

Fifteen specimens were examined in this fashion and in six of them typical holes were found grossly In the other nine cases the bronchoscopist designated the openings seen as "crypts" These are considered as common findings—small shallow out pouchings or depression of the bronchial mucosa The patients from whom these specimens had been taken varied in age from 37 to 82 years Only one of them had advanced pulmonary tuberculosis and no hole was found in this case Patients with positive findings died of a variety of causes, most of them unrelated to pulmonary disease Five had signs of severe chronic bronchitis

Histologic examinations were carried out on multiple blocks and some of them were sectioned in steps Neighbouring sections were stained with hematoxylin-eosin and elastica-van Gieson Basically a similar picture was found in all lesions examined and no clear-cut histologic differentiation was possible between so-called crypts and mucosal holes The lesions represented either widened ducts of mucous glands, cone-shaped or flask-shaped, with narrow mouths, (Fig 3) or globular depressions widely communicating with the bronchial lumen (Fig 4) Inflammatory changes were present either in the depth of the ducts or at their necks Some of the lesions showed no inflammatory changes At times, the bronchial muscles were hypertrophic, forming a thickening at the neck of a dilated duct In the depth of the ducts and depressions, mucous glands were noted, some with mild chronic inflammatory infiltration, some without significant histologic changes and some with signs of mild atrophy

FIGURE 4 Crypt with wide neck Inflammatory and other changes as in Figure 3

In our limited material, we never saw association of these dilated ducts with disease of adjacent bronchial lymph nodes At times, anthroco-silicotic or fibrotic lymph nodes were found attached to the bronchial walls in areas of ductal dilatation but from the histologic appearance this association was considered fortuitous

These anatomic findings confirmed our opinion that most of the mucosal holes found were actually diseased excretory ducts Other facts pointed in the same direction Careful tomographic examination especially of the hilar region of our 49 patients failed to reveal enlargement of lymph nodes, nor were there pathognomonic clinical or roentgenologic signs of recent perforation By far the greatest number of orifices noted were covered with normal mucosa and showed only mucous secretion But also in cases showing signs of inflammation, purulent secretion or small translucent granulations, these changes were probably caused by an infection of the dilated ducts, since all these changes had disappeared on subsequent examinations There remained, ultimately, only a hole covered by normal mucosa The fact that the appearance of these openings did not change even after one or two years also seems to indicate that they were not due to bronchial fistulae

In 22 patients the mucosal holes were situated in the bronchus leading toward the main lesion It is true that lymph node perforation at this location may be responsible for the development of such a lesion, on the other hand mucous gland involvement may be caused by the regional parenchymatous process, so that this localization is not sufficient to differentiate the nature of the bronchial lesion

Only in seven of our patients was a lymph node perforation suspected although none of them showed the pathognomonic bronchoscopic appearance Holes were seen in all of them, some of which were more than 3 mm in diameter, and nearly all showed signs of severe inflammation and purulent secretion for a long time Where repeated control examinations were done, we observed that healing took place with scar formation In addition, the clinical and/or roentgenologic findings suggested an active specific process of the hilar lymph nodes Of these seven adults, one suffered from primary tuberculosis, in four others the pulmonary lesions were considered as direct sequelae of the primary infection (post-primary lesions) and only two patients suffered from a chronic phthisic form of tuberculosis Appearance and development of the lesions is demonstrated by the following two typical cases

Case 1 A 26 year old woman from Hungary was admitted following an acute episode of fever, cough and weight loss X-ray film examination showed calcified lymph nodes between the right upper and middle lobes and confluent patchy lesions with a prune-shaped cavity in the postero-lateral segment of the right lower lobe At the first bronchoscopy in January 1953, a hole was noted at the entrance of the right upper lobe bronchus, measuring 1 x 2 mm in diameter, partially covered by granulation tissue Control bronchoscopies at 3-month intervals disclosed a continuous diminution in the size of the hole with epithelization in its depth In May 1954, only a funnel-shaped scar remained with dilated capillaries traversing the area At this stage, a resection of the right lower lobe was performed During operation, a group of enlarged soft lymph nodes was palpated around the bronchi of the middle and upper lobes

Conclusion In this patient a cavernous pulmonary process in the right lower lobe was probably a sequela of a bronchogenous dissemination from perforated lymph nodes A residual perforation in the right upper lobe bronchus healed in the course of a year

Case 2 On routine examination, a cavernous pulmonary process was discovered in a 30 year old man from Rumania There were no clinical symptoms, but tubercle bacilli were found in the sputum on rare occasions The roentgen picture, on admission, revealed widespread infiltrative and dense peribronchial changes in the apical and posterior segments of the right upper lobe Calcified lymph nodes were noted close to the posterior wall of the right upper lobe bronchus On bronchoscopic examination a crater-shaped opening, the size of a rice grain, was found on the medial wall of the right main bronchus 2 cms below the carina The floor of the defect was covered with purulent secretion Under antimicrobial treatment, constant improvement of pulmonary and bronchial changes was noted Five months following the first bronchoscopy, the floor of the defect was covered by smooth granulation tissue and the size of the opening diminished gradually After 15 months, there was only a mucosal scar left with a central depression and capillary dilatation The pulmonary process, at that time was apparently arrested, the peribronchial changes had completely disappeared

Conclusion The bronchoscopic appearance was highly suggestive of hilar lymph node perforation The pulmonary and peribronchial changes in the right upper lobe might have been related to the lymph node lesion Both lesions healed concomitantly

Discussion

In an analysis of 700 consecutive bronchoscopies on adults suffering from pulmonary tuberculosis we were unable to find a single case showing the pathognomonic picture of recent lymph node perforation into the bronchial lumen However, we observed a great number of pathologic changes in the bronchial mucosa that could be classified as either suggestive or indirect signs of lymph node perforation With regard to the latter there arises the question, if we are allowed to draw the conclusion that lesions like stenosis, granulations, superficial ulcerations or slight alterations in the appearance of the bronchial mucosa are invariably caused by perforation of a tuberculous lymph node, even in the presence of so called typical clinical and roentgenologic findings The involvement of the bronchial tree by a tuberculous process may occur through various pathways Extension of an inflammatory process from adjacent structures, direct implantation of contaminated material from the lumen, hematogenous and lymphogenous dissemination into the bronchial wall, lymph node perforation is only one of the possible pathogenic mechanisms [1, 16] For these reasons we excluded 58 cases with stenosis, granulations, ulcerations or "cushions" from further analysis and we accepted only star-shaped or funnel-shaped retractions of the bronchial mucosa as possible remnants of a former lymph node perforation We observed eight such cases in our series

As for so-called suggestive signs of lymph node perforation, we collected 64 cases with abnormal openings in the bronchial mucosa, an incidence similar to that reported from other institutions, especially those that differentiate between definite perforations and mucosal holes, as e g Glittre Sanatorium (8 per cent)

In only seven of our patients we suspected perforations of a tuberculous lymph node into the bronchial wall

The low incidence in our material may be due in part to a different patient population Most of our patients were new immigrants, adults with chronic pulmonary tuberculosis of long standing In institutions, where more adolescents are admitted, suffering from the primary or post-primary phase of tuberculosis typical lymph node perforations will undoubtedly be observed with greater frequency

The basic divergence, however, derives from a different interpretation of the bronchoscopic findings We wonder whether many holes or so-called fistulae included in the records of other authors, are not actually diseased excretory ducts Pathologic changes in the bronchial glands with consequent cystic degeneration of the glands or enlargement of the ducts occur certainly much more frequently in the adult than perforation of caseous lymph nodes Especially persons with long standing infections of the respiratory tract and certainly those suffering from pulmonary tuberculosis are liable to develop these changes We saw, of course, such lesions also in non-tuberculous patients with chronic inflammatory changes in the respiratory tract, e g with chronic bronchitis, asthma and emphysema Of the six autopsy specimens with the typical holes, five showed evidence of severe chronic bronchitis With contrast filling of the bronchial tree, we were able to demonstrate the typical picture of ductal dilatation in a great many patients suffering from chronic cough, pointing possibly to a pathogenetic relationship

Differentiation between lymph node perforation and enlarged glandular ducts is often difficult only on bronchoscopic appearance In rare instances, an actual perforation may heal and present a normal mucosal covering On the other hand, active pathologic changes may occur within enlarged mucosal ducts in the absence of lymph node perforations Infectious material may gain entrance into the glandular duct from the bronchial lumen and give rise to inflammatory changes within the glands

In doubtful cases one must not rely on one single bronchoscopy Additional clinical and roentgenologic data must be evaluated before a definite opinion is formed If, on control examinations, signs of inflammation disappear and the caliber of the opening remains unchanged for a long period the lesion is probably an enlarged duct

A correct diagnosis of lymph node perforation is, however, of great importance since it has serious implications for the patient Major operations e g may have to be postponed for months An active perforation, persisting after resection may lead to reactivation or spread of the specific process Careful bronchoscopic evaluation is therefore mandatory prior to operation and in doubtful cases, it is better to repeat the examination in order to ascertain the character of the bronchial lesion noted

Lymph node perforation in the adult in all stages of the disease does, of course, occur though it is rare Seven of our observations probably belong to this category The bronchoscopic observations alone were highly suggestive and they were further supported by clinical and/or roentgenologic signs of active tuberculous disease in adjacent lymph nodes In the eight

cases, showing only residual scars, there was found a distinct correlation between the scar and the dominant pulmonary lesion In five of these cases a calcified lymph node could be seen adjacent to the bronchial scar Still, there was no indication as to the time of the lymph node perforation It might have taken place much earlier, even during childhood

Conclusion

In our experience, perforations of tuberculous lymph nodes into the bronchi are rarely observed on bronchoscopic examination of the adult, especially in patients suffering from the chronic phthisic form of pulmonary tuberculosis Mucosal holes, however, as seen through the bronchoscope are more frequent and are apt to be diseased excretory ducts rather than fistulous tracts from caseous lymph nodes We doubt therefore, that reports of frequent bronchoscopic diagnosis of lymph node perforation are convincing proof for the validity of Schwartz' concept of re-infection tuberculosis Further clinical, bronchoscopic and careful anatomic studies are necessary in order to decide whether perforations of lymph nodes in all stages of adult tuberculosis are so common as to require a change in our views concerning the pathogenesis of the disease

SUMMARY

Seven hundred consecutive bronchoscopies were analyzed for evidence of lymph node perforation into the bronchial tree without finding a single case with the pathognomonic appearance Lesions suggestive of perforation were seen in seven cases and eight presented characteristic scars Additional clinical and roentgenologic data corroborated the diagnosis in these 15 cases

Pathologic openings in the bronchial mucosa were found with about the same frequency as in other institutions (8 per cent) Bronchoscopic, roentgenologic and anatomic features of these lesions are reviewed and described and their pathogenesis is discussed

The difficulties in the interpretation of the bronchoscopic appearances of fistulous tracts due to lymph node perforation and diseased excretory ducts of mucous glands are noted

RESUMEN

Se hicieron 700 broncoscopias consecutivas en busca de evidencias de perforación de ganglios hacia el árbol bronquial sin encontrar un solo caso patognomónico por la apariencia Se vieron lesiones sugestivas de perforación en siete casos y ocho presentaban cicatrices características Los datos clínicos y roentgenológicos adicionales corroboraron el diagnóstico en estos 15 casos

Se encontraron aberturas patológicas en la mucosa bronquial con la misma frecuencia aproximada que en otras instituciones (8 por ciento)

Remark By the time this article was completed, another 400 bronchoscopies had been analyzed, bringing the total of patients examined to over one thousand Whereas the relative number of mucosal holes remained fairly constant (7 to 8 per cent) we did not find a single case of definite or suspected lymph node perforation

Las caracteristicas broncoscópicas, roentgenológicas y anatomicas de estas lesiones son objeto de revisión y su patogenia se discute

Las dificultades en la interpretación de la apariencia broncoscópica de los conductos fistulosos debidos a perforación ganglionar y la distinción con los conductos excretorios enfermos, se hacen notar

RESUME

700 bronchoscopies consecutives furent analysées pour rechercher la preuve de la perforation ganglionnaire dans l'arbe bronchique sans qu'on puisse trouver un seul cas indiscutable La perforation pouvait être suspectée dans sept cas et huit autres présentèrent des cicatrices caractéristiques Des constatations cliniques et radiologiques supplémentaires furent en faveur du diagnostic dans ces quinze cas

Ces perforations pathologiques de la muqueuse bronchique se présentèrent avec environ la même fréquence que dans les autres conditions (8%) Les caractéristiques bronchoscopiques, radiologiques et anatomiques de ces lésions sont passées en revue et décrites et l'auteur discute leur pathogénie

Il signale les difficultés d'interprétation bronchoscopique des fistules imputables à une perforation ganglionnaire et des conduits excrétoires des glandes muqueuses

ZUSAMMENFASSUNG

Es wurden 700 auf einander folgende Bronchoskopien analysiert auf Beweise einer Lymphknotenperforation in den Bronchialbaum ohne dass ein einziger Fall gefunden wurde mit pathognomonischen Erscheinungen

Auf Perforation verdachtige Veranderungen waren in 7 Fallen zu sehen, und 8 boten charakteristische Narben Zusatzliche klinische und rontgenologische Daten bestatigten die Diagnose in diesen 15 Fallen

Pathologische Öffnungen in der Bronchialschleimhaut wurden in ungefahr derselben Haufigkeit gefunden, wie in anderen Anstalten (8%) Bronchoskopische, rontgenologische und anatomische Merkmale dieser Veranderungen werden besprochen und beschrieben und ihre Pathogenese diskutiert

Die Schwierigkeit in der Deutung des bronchoskopischen Aussehens der Fistelgange infolge Lymphknotenperforation und erkrankter Ausfuhrungsgange der Schleimdrusen wird erwahnt

REFERENCES

1 Kraan, J K and Muller, S "Perforation of Tuberculous Glands into a Bronchus," *Acta Tuberc Scandinav*, 24 88, 1950

2 Schwartz, Ph "Ein bruche tub Lymphknoten in das Bronchialsystem u ihre pathogenetische Bedeutung," *Beitr z Klin d Tub*, 103 182, 1950

3 Schwartz, Ph "Signification pathogenique des perforations lympho-glandulaires intrathoraciques au point de vue de la phtisie pulmonaire et des ses complications," *Le Poumon*, 6 379, 1950

4 Schwartz, Ph "The Role of the Lymphatics in the Pathogenesis of Bronchogenic Tuberculosis," *Transactions Nat Tub Ass*, pp 202-216, 1952

5 Uhlinger, E "Die Path Anatomie der Bronchustuberkulose," *Bibl Tuberculosa*, 1 31, 1950

6 Levi-Valensi, A, Zaffran A et Molina C "24 Cas de fistules ganglio-bronchiques chez les tuberculeux pulmonaires adultes," *Rev de la Tubere*, 15 410, 1951

7 Vaksvik, P "Primary Bronchial Tuberculosis in Adult Sanatorium Patients," *Acta Tub Scand*, 27 255, 1952

8 Iselin H and Suter F "The Role of Perforations of Hilar Lymph Nodes into the Bronchial Tree of Adults," *Dis Chest*, 25 302, 1954

9 Meng, G "Zur Diagnose der Residuen von tuberkulosen Bronchial-Lymphknotenperforationen im Bronchialbaum," *Schweiz Z Tub*, 12 446, 1955

10 Tricoire, G "Fistules ganglio-bronchiques en dehors de la Primo-Infection," *Rev de la Tubere*, 19 559, 1955

11 Chatonnier J et Zaffran, A *J de Pneumophtisiol de l'Afrique du Nord*, 3 264, 1951

12 Popper, M, Davidsohn, S, Eskmazy, Ys, Camil, A, Finkelstein, M et Gheorghiu, T "Les fistules ganglio-bronchiques hors l'infection primaire evolutive," *Rev de la Tubere*, 20 380, 1956

13 Huizinga, E and Smelt, G J *Bronchography* Van Gorcum, Assen Netherlands 1949, pp 207-208

14 Duprez A and Mampuys, R "Cystic Enlargement of the Mucous Glands of the Bronchus Associated with Chronic Bronchitis," *Thorax*, 8 141, 1953

15 Adler, H "Phtisiogenic Considerations Based on Tomographic Analysis of 320 Consecutive Cases of Localized Pulmonary Tuberculosis in Adults," *Dis Chest*, 24 191, 1953

16 Dykstra, C *Atlas of Bronchial Lesions in Pulm Tubere* Charles C Thomas, Springfield, Ill, U S A 1955

SECTION ON CARDIOVASCULAR DISEASES

Results of Open Heart Surgery with Elective Cardiac Arrest by Potassium Citrate in Patients with Congenital and Acquired Heart Disease*

F MASON SONES, JR, M D, F C C P
Cleveland, Ohio

The use of elective cardiac arrest in combination with a pump oxygenator makes possible better surgical exposure of the internal structure of the heart than has ever before been achieved Melrose[1] and associates in 1955 reported a simple technique for stopping the heart by the use of potassium citrate solution in laboratory animals Work in our laboratory[2] confirmed that a mixture of twenty-five per cent potassium citrate solution, diluted one part to ten with blood, would produce complete asystole when injected into the coronary circulation

The heart is isolated from the systemic circulation by occlusion of the vena cavae, and clamping the ascending aorta, after establishing the usual cannulations for maintenance of the circulation with a pump oxygenator The potassium solution is injected into the root of the aorta proximal to the clamp, so that it rapidly perfuses the coronary circulation Complete asystole, with a soft, flaccid heart, occurs as soon as total perfusion of the coronary artery bed has been accomplished The heart remains in asystole until the aortic clamp is removed, permitting the potassium solution to be washed out of the coronary circulation by arterialized blood from the pump oxygenator Adequate perfusion of the coronary arteries with arterialized blood, under essentially normothermic conditions, results in a prompt return of normal heart rhythm

Achievement of adequate surgical exposure for as long as 60 minutes in a quiet, reasonably dry field, inside any of the heart chambers, appeared to offer nearly unlimited possibilities for the correction of intra-cardiac mechanical deformities Since February, 1956, 80 open cardiotomies have been performed by Dr Donald B Effler and associates utilizing elective cardiac arrest and one of four different pump oxygenators under the supervision of Dr Willem Kolff

The purpose of this report of initial results, presented from the viewpoint of a medical observer, is to record the successful results, and point out some of the reasons for clinical failure Diagnostic and technical surgical problems will be stressed because these are most easily recognized,

*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

**From the Department of Cardiovascular Disease, The Cleveland Clinic Foundation and the Frank E Bunts Institute

but it is evident that some of the most difficult and unresolved aspects of the overall problem remain in the field of prolonged total body perfusion A lively and healthy controversy, beyond the scope of this report, still rages among the proponents of various oxygenators, and supports the belief that a truly ideal method remains to be found

The anatomic problems dealt with, and the mortality encountered in each group are listed in Table I While the basic nature of the defect has an important bearing on surgical mortality, this does not reflect other important factors such as age, body mass, myocardial reserve, anoxia, pulmonary vascular disease, and degenerative changes in the systemic circulation, which often proved to be crucial factors in achieving success or failure within each group The largest number of patients (62 5 per cent) had interventricular septal defects or Tetralogy of Fallot Nine patients had acquired lesions, including one with an interventricular septal defect due to septal myocardial infarction The remainder were congenital in origin The patients ranged in age from two months to 58 years Body weight varied between seven and 190 pounds

Cardiac catheterization was performed on all patients pre-operatively During catheterization, selective cardioangiograms were photographed on 35 mm motion picture film at 54 frames per second, using a 5 inch image amplifier This could not be done successfully in many adult patients with very large hearts, but proved to be helpful in establishing anatomic diagnoses in children

TABLE I

	Diagnosis	Patients	Survived	Dead
1	Interventricular Septal Defect	31	21	10
2	Tetralogy of Fallot	19	12	7
3	Interatrial Septal Defect			
	(a) Ostium Primum with Mitral Regurgitation	4	2	2
	(b) Ostium Secundum with Mitral Stenosis	2	0	2
	(c) Ostium Secundum	2	1	1
	(d) With Anomalous Pulmonary Veins	1	0	1
4	Valvular Pulmonic Stenosis			
	(a) With Intact Septa	1	1	0
	(b) With Interatrial Septal Defect	2	2	0
5	Infundibular Pulmonic Stenosis with Intact Septa	1	1	0
6	Aortic Stenosis			
	(a) Congenital	2	2	0
	(b) Rheumatic	5	1	4
7	Mitral Regurgitation			
	(a) Ruptured Chordae Tendineae	1	1	0
	(b) Congenital Cleft-anterior Leaflet	1	1	0
	(c) Rheumatic	2	0	2
8	Corrected Transposition of Great Vessels			
	(a) Single Ventricle	1	0	1
	(b) Pulmonic Stenosis and Multiple Interventricular Septal Defects	1	0	1
9	Pulmonary Hypertension			
	(a) Suspected Intra-cardiac Tumor	1	0	1
10	Transposition of Great Vessels	3	0	3
	TOTAL	80	45	35

Interventricular Septal Defects

Thirty one patients were selected for closure of interventricular septal defects Utilizing cine-cardioangiography, an attempt was made to demonstrate the relationship of the aortic and pulmonary valve rings to the plane of the ventricular septum Patients with evidence of more than 50 per cent dextraposition of the aorta, and those in whom the lesion anatomically was proved pre-operatively to be a single ventricle were excluded as candidates for surgery Those with small shunts (pulmonary blood flow less than twice the volume of systemic blood flow) and resting pulmonary artery systolic pressures below 45 mm Hg were not considered surgical candidates

Patients were divided into two groups depending on the presence or absence of severe pulmonary hypertension

TABLE II—INTERVENTRICULAR SEPTAL DEFECTS WITH PULMONARY HYPERTENSION

(Pulmonary Artery Pressure Higher Than 70 Per Cent of Systemic Pressure)

				Pressure		Oxygen Pulmonary A-V Difference	
		Age	Weight	P A	F A	Systemic A-V Difference	Result
1	H K	7 yrs	50 lbs	74/40	106/62	0 45/1 9	Defect closed
2	J M	5 yrs	26 lbs	124/64	140/62	1 75/3 5	Defect closed
3	C C	3 yrs	30 lbs	80/16	115/60	1 4/4 4	Defect closed
4	C J	2 yrs	30 lbs	75/33	95/54	1 0/2 4	Defect closed
5	W Z	4 yrs	29 lbs	112/64	117/73	2 0/3 55	Defect closed
6	M E	11 mos	14 lbs	87/30	78/44	2 9/5 5	Coarctation excised Possible incomplete closure
7	R G	4 yrs	29 lbs	76/35	92/68	0 9/3 2	Defect closed
8	R P	4 yrs	33 lbs	84/41	102/52	1 6/4 05	Defect closed[r]
9	L C	4 yrs	29 lbs	89/42	110/55	3 6/4 5	Died—congestive failure Pulmonary vascular disease
10	L R	2 yrs	25 lbs	88/2	104/48	7 6/3 0	Died—fibroelastosis Pulmonary vascular disease
11	M D	4 yrs	35 lbs	86/50	92/42	4 0/4 0	Died—congestive failure Pulmonary vascular disease
12	J K	6 mos	9 lbs	88/48	92/58	0 9/2 65	Died—anoxia Pulmonary cystic disease
13	J P	11 yrs	58 lbs	85/54	108/65	1 5/3 3	Died—subacute bacterial endocarditis
14	N W	27 yrs	125 lbs	108/64	113/70	0 5/5 2	Died—single ventricle Incomplete closure A-V block

[r] Post-operative catheterization

Fourteen patients (Table II) had measured pulmonary artery pressures which exceeded 70 per cent of systemic pressures The relationship between pulmonary and systemic blood flows was carefully evaluated, and proved to be a most important factor in determining the presence or absence of irreversible pulmonary vascular disease Actual blood flow measurements could not be made because many of the patients were too young to cooperate in the measurement of oxygen consumption It was possible, however, to measure pulmonary and systemic arterio-venous oxygen differ-

TABLE III—INTERVENTRICULAR SEPTAL DEFECT WITH MODERATE PULMONARY HYPERTENSION
(Pulmonary Artery Pressure Lower Than 70 Per Cent Systemic Pressure)

		Age	Weight	Pressure P A	Pressure F A	Oxygen Pulmonary A-V O_2 Difference / Systemic A-V O_2 Difference	Result
1	B I	16 mos	16 lbs	58/20	90/50	0 7/3 4	Defect closed
2	R M	8 yrs	11 lbs	32/16	108/62	2 0/4 4	Defect closed
3	J G	5 yrs	38 lbs	57/20	112/62	0 9/3 7	Defect closed*
4	D C	3 yrs	24 lbs	35/14	112/62	1 7/4 3	Defect closed
5	N S	3 yrs	32 lbs	66/20	134/60	0 4/3 3	Defect closed*
6	K B	18 mos	21 lbs	54/21	102/55	0 8/3 3	Defect closed*
7	R D	5 yrs	34 lbs	42/11	108/50	1 1/3 3	Shunt persists*
8	M H	7 yrs	40 lbs	52/28	112/70	2 1/4 0	Defect closed
9	C E	22 mos	28 lbs	55/20	109/50	1 75/2 3	Probable incomplete closure
10	K M	3 yrs	31 lbs	67/21	110/50	1 1/3 0	Defect closed*
11	M C	3 yrs	32 lbs	45/11	118/50	3 0/4 1	Defect closed
12	P L	4 yrs	37 lbs	60/25	132/90	0 7/3 1	Defect closed
13	F G	48 yrs	152 lbs	63/23	136/92	1 1/4 6	Septal infarction Possible incomplete closure
14	W H	15 mos	21 lbs	42/20	96/52	2 75/5 6	Died—right ventricle occluded
15	B R	7 mos	7 lbs	42/22	87/43	0 9/3 3	Died—A-V block Multiple I V S D plus I A S D
16	T P	9 yrs	38 lbs	52/14	112/68	1 7/2 9	Died—respiratory acidosis Severe kyphoscoliosis Myocardial necrosis
17	J K	3 yrs	27 lbs	68/20	102/58	3 3/5 7	Died—focal myocardial necrosis

* Post-operative cardiac catheterization

ences When the pulmonary A-V difference is lower than systemic A-V difference, pulmonary blood flow exceeds systemic flow, and high pulmonary artery pressures may be expected to fall with successful closure of the shunt If the pulmonary A-V oxygen difference approximates or exceeds the systemic A-V oxygen difference, pulmonary hypertension is due to high pulmonary vascular resistance, and closure of the septal defect cannot result in a return toward normal dynamics Three of the 14 patients with severe pulmonary hypertension presented this picture (Table II, 9, 10, and 11) All died in the immediate post-operative period Of the 11 who demonstrated *high* pulmonary flows, three died, one of bacterial endocarditis (Table II, 13), one because he proved to have a single ventricle which was an impossible technical problem (Table II, 14), and one (a six month nine pound infant) of ventilatory insufficiency complicated by cystic disease of the lungs (Table II, 12)

Of eight surviving patients with severe pulmonary hypertension, clinical evidence of successful closure is present in seven In two of these, anatomic correction has been confirmed by post-operative catheterization and cardioangiograms One patient in this group shows clinical manifestations of a residual left to right shunt

Of 17 patients with pulmonary artery pressures lower than 70 per cent of systemic pressures, 13 (76 4 per cent) survived operation (Table III)

Four patients in this group died four hours to seven days after operation

1 (Table III, 14) This child had an anomalous papillary muscle or moderator band, which crossed but did not obstruct the right ventricular outflow tract pre-operatively It was carefully preserved and the defect was closed The child died in acute right heart failure eight hours later At post mortem examination, the muscle was found obstructing the right ventricular outflow tract, which was reduced in diameter as a result of closure of the septal defect Similar problems, encountered since, have been solved by excision of such moderator bands without recognizable sequellae

TABLE IV—INTERVENTRICULAR SEPTAL DEFECT
(Pre- and Post-operative Catheterization Data)

			Arterial O Per Cent Saturation	Pulmonary Artery Pressure	Systemic Pressure	Oxygen Pulmonary A-V O Difference / Systemic A-V O_2 Difference
1	J M	pre-op	86	124/64	140/62	1 75/3 5
	(5 yrs) 9 mos	post-op	94	41/11	110/55	2 8/2 8
2	R P	pre-op	90	84/47	102/55	1 6/4 1
	(4 yrs) 8 mos	post-op	94	39/10	104/60	3 7/3 7
3	N S	pre-op	88	66/20	134/60	0 4/3 3
	(3 yrs) 7 mos	post-op	95	30/13	132/64	3 2/3 2
4	K M	pre-op	90	67/21	103/50	1 1/3 0
	(3 yrs) 9 mos	post-op	95	36/6	124/62	4 1/4 1
5	J G	pre-op	92	57/20	112/54	0 9/3 7
	(5 yrs) 7 mos	post-op	96	31/13	118/60	2 8/2 8
6	K B	pre-op	84	54/21	102/55	0 8/3 3
	(18 mos) 7 mos	post-op	90	18/9	100/58	2 55/2 55
7	R D	pre-op	93	42/11	108/50	1 1/3 3
	(5 yrs) 7 mos	post-op	94	35/12	118/56	0 6/3 5

2 (Table III, 15) A seven month infant weighing seven pounds was known to have a diaphragmatic hernia in addition to separate interventricular and interatrial septal defects At operation she proved to have two ventricular defects instead of a single one anticipated Both septa were closed After the heart was allowed to beat, she showed persistent hypotension, hypoxia, and A-V block She never regained consciousness Small body mass and inability to maintain adequate ventilation contributed to the problem

3 (Table III, 16) This girl had severe kyphoscoliosis Her septal defect was easily closed Post-operatively she developed biochemical changes characteristic of severe respiratory acidosis Despite every effort at mechanical assistance, this could not be controlled On the fifth post-operative day, progressive congestive manifestations appeared and she died on the seventh day Post mortem examination revealed severe focal myocardial necrosis, which to date, remains unexplained

4 (Table III, 17) A three year old boy developed persistent supra-ventricular tachycardia four hours after a satisfactory sinus rhythm had been established He died suddenly 10 hours after operation Post mortem examination revealed medial hypertrophy of the pulmonary arterioles, but no intimal changes There was severe acute focal myocardial necrosis, which is unexplained

The latter two patients present a problem which we believe is related to artificial perfusion We do not believe this is due to the use of potassium citrate, since we have seen it in patients who have had artificial perfusion without induced cardiac arrest

Of 13 surviving patients with mild to moderate pulmonary hypertension, 10 have had anatomic closure of the defect In two, clinical study indicates that incomplete closure has been obtained, and in one, post-operative catheterization demonstrated persistence of the defect

Table IV shows the post-operative catheterization data of seven patients from both groups seven to nine months following operation All but one have had excellent surgical results with gratifying reductions in pulmonary artery pressure and eradication of shunts

Table V summarizes the results in 31 patients of both groups In Group I (patients with severe pulmonary hypertension) no patient with low pulmonary artery flow survived the immediate post-operative period On the other hand, the results in Group I patients with high pulmonary flows approximated those obtained in patients with lower pulmonary pressures The presence of pulmonary hypertension, therefore, should *not* be considered a valid contra-indication to surgery unless it is also demonstrated that

TABLE V—INTERVENTRICULAR SEPTAL DEFECTS—31 PATIENTS

GROUP I—Pulmonary Artery Pressure Higher Than 70 Per Cent of Systemic Pressure	No	Survived		Dead	
		No	Per Cent	No	Per Cent
A Low Pulmonary Blood Flow	3	0	0	3	100
B High Pulmonary Blood Flow	11	8	72 8	3	27 2
TOTAL	14	8	57 2	6	42 8
GROUP II—Pulmonary Artery Pressure Lower Than 70 Per Cent of Systemic Pressure	No	Survived		Dead	
		No	Per Cent	No	Per Cent
High Pulmonary Artery Flow	17	13	76 4	4	23 6
TOTAL—Groups I and II	31	21	67 8	10	32 2

1 Pulmonary artery blood flow is low because of far advanced pulmonary vascular disease
2 The aorta or pulmonary artery is too far transposed to permit closure of the defect
3 The patient has a single common ventricular chamber, which at present constitutes an impossible technical problem for surgical correction

Tetralogy of Fallot

The 19 patients classified as Tetralogy of Fallot all had interventricular septal defects with one or more obstructions in the right ventricular outflow tract causing a systolic pressure gradient between the right ventricle and pulmonary artery In some there was significant overriding of the aorta, but in most the aorta arose entirely from the left ventricle Right to left shunts were present at rest in all but one patient Two patients had co-existing left to right shunts The type of stenosis was classified as valvular in two, infundibular in 10, infundibular and valvular in six, and infundibular with hypoplastic valve ring in one patient

At operation this group of patients showed incredible variations in internal structure, and it has become progressively more evident that the goal of restoration to normal cardio-dynamics is more easily discussed than achieved Seven patients (36 per cent) died five hours to 31 days post-operatively The causes of death were defined as follows

1 Agenesis of the left pulmonary artery was unrecognized by pre-operative studies Death due to anoxia
2 Persistent complete A-V heart block occurred following car-

TABLE VI—TETRALOGY OF FALLOT
(Pre- and Post-operative Catheterization Data)

				Pressures		Arterial O Per Cent Saturation	Pulmonary A-V Difference / Systemic A V Difference
				R V	P A		
1	R B		pre-op	104/3	12/6	82	4 8/2 9
	(6 yrs)	13 mos	post-op	38/2	37/25	97	3 5/3 5
2	P B		pre-op	77/2	31/15	81	3 35/1 6
	(5 yrs)	9 mos	post-op	27/2	27/13	97	3 9/3 9
3	R W		pre-op	92/2	22/12	77	9 3/5 2
	(9 yrs)	6 mos	post-op	87/7	44/10	92	2 7/3 8
4	M C		pre-op	89/4		72	6 5/3 0
	(14 mos)	7 mos	post-op	108/6	38/10	94	3 9/5 6
5	D L		pre-op	108/6	17/2	88	5 7/4 6
	(5 yrs)	8 mos	post-op	140/6	38/12	90	3 0/4 2
6	D B		pre-op	104/3		81	9 7/6 0
	(12 yrs)	4 mos	post-op	98/3	34/8	97	3 4/4 6
7	R G		pre-op	116/6	24/12	74	10 1/6 5
	(10 yrs)	4 mos	post-op	78/10	57/17	93	2 2/3 4
8	J D		pre-op	115/9	35/17	92	2 3/3 2
	(8 yrs)	8 mos	post-op	118/12	110/42	92	2 6/6 6

diac resuscitation in two patients One died with hypotension, severe anoxia, and intractable bradycardia 12 hours after operation The other died suddenly 31 days post-operatively after a slow and difficult recovery from operation

3 Cerebral edema led to generalized muscle spasm, positive pyramidal tract signs, and death five hours post-operatively There were no generalized systemic changes The exact cause remains obscure

4 Sudden death due to asystole 12 hours after operation occurred immediately following tracheal aspiration Post mortem examination revealed wide excision of infundibular pulmonic stenosis and closure of ventricular septal defect There were no congestive changes No obstruction was present in the tracheo-bronchial tree

5 Rapid development of pulmonary congestive changes, hypoxia, and death 20 hours after operation occurred in one child Post mortem examination revealed severe acute focal myocardial necrosis The cause is unknown

6 Persistent cyanosis, supraventricular tachycardia, and progressive pulmonary congestive changes occurred in one child who died 30 hours after surgery Post mortem examination was not permitted

Of 12 surviving patients, 10 show clear-cut evidence of *functional* improvement, as judged by disappearance of cyanosis and polycythemia, regression of digital clubbing, and a remarkable increase in physical capacity for exercise We were concerned about an associated increase in overall heart size which has persisted in nine patients

Eight patients have been catheterized four to 13 months since operation Table VI summarizes the results of this study Complete anatomic and physiologic correction has been achieved in two patients (Table VI, 1 and 2) In four patients (3, 4, 5, and 6) the interventricular septal defect remains open, and pulmonary blood flow has been increased because of a reduction in the severity of obstruction in the right ventricular outflow tract A significant degree of stenosis persists, however, protecting the pulmonary vascular bed from the full effects of high pressure and flow Patient number seven still has a large interventricular septal defect with more effective excision of his infundibular stenosis He has moderate pulmonary hypertension Although his cyanosis has disappeared, his activity tolerance has not improved in the same degree as that noted in the first six patients Patient number eight developed congestive heart failure three weeks post-operatively She still has a large septal defect with severe pulmonary hypertension because there is no residual obstruction at the pulmonary valve Her functional status has deteriorated and a second attempt to close the septal defect is planned in the near future

From the above it would appear that the severity of right ventricular outflow tract obstruction may be relieved, but that closure of interventricular septal defects in patients with Tetralogy of Fallot is a much more

difficult problem than that presented by uncomplicated septal defects

It is our belief that failure to bridge the gap of the defect with a prosthesis is responsible for these technical failures Although it is usually unnecessary and undesirable to use a foreign body for closure of uncomplicated ventricular defects, this course is now being followed in patients with Tetralogy of Fallot

Interatrial septal defect was thought to be the primary lesion in nine patients who required elective arrest

Ostium primum defects with mitral regurgitation have been encountered in four patients

1 The significance of mitral regurgitation was not appreciated in a seven year old boy with a large left to right shunt at the atrial level His septal defect was carefully closed, avoiding both the mitral and tricuspid valves Post-operatively he had persistent A-V heart block and developed progressively severe pulmonary congestive changes which could not be controlled by medical management Mitral regurgitation was recognized as the basic cause of his increasing difficulties, but his heart block and pulmonary status precluded re-operation Post mortem examination revealed a cleft in the aortic leaflet of the mitral valve His atrial septal defect was closed The lungs showed hemorrhagic pulmonary edema

2 A 12 year old boy presented a similar picture to that noted above His atrial defect was closed and he rapidly developed congestive manifestations and orthopnea Heart catheterization showed a rise in pulmonary artery pressure from 23/6 mm Hg, before closure of his atrial defect, to 57/26 mm Hg Pulmonary artery wedge pressures rose from 8 mm pre-operatively to 26 mm His left to right shunt had been abolished A second open cardiotomy was performed via the left atrium A crescent shaped prosthesis was sutured over the medial commissure of the mitral valve around the valve annulus This effectively controlled the localized type of regurgitation present His recovery from the second period of elective cardiac arrest was remarkably prompt His heart size has been reduced by 25 per cent *All congestive manifestations have* disappeared

3 Mitral regurgitation due to a grossly dilated mitral valve ring was recognized at operation in a 17 year old boy with an interatrial defect The medial commissure of the valve was partially closed by direct suture The atrial defect was closed He developed pulmonary edema and died 18 hours later Post mortem examination revealed that both suture lines were fragmented

4 Mitral regurgitation was found to be present in a 50 year old man with an ostium primum defect An Ivalon sponge prosthesis was sutured to the mitral valve annulus above the medial commissure, and the defect was closed He has made an excellent recovery

These patients demonstrate the importance of recognizing and correcting *mitral regurgitation when it co-exists with interatrial septal defects* The combination is not unusual Exact pre-operative diagnosis of this combination of lesions is at present difficult and unreliable Careful examination of the mitral valve in every patient before proceeding with closure of interatrial defects appears to be the surest method of diagnosis available at this time

Ostium secundum defects with mitral stenosis (Leutembacher's syndrome) have been encountered on two occasions

1 A seven month infant weighing 10 pounds proved to have congenital mitral stenosis and a large interatrial septal defect with a left to right shunt at the atrial level Congestive manifestations could not be controlled on medical management The mitral valve was approached through the defect from a right atrial cardiotomy The valve was split by finger fracture and the atrial defect was closed Despite tracheotomy, it was impossible to keep the lungs adequately expanded and the child died on the sixth post-operative day At post mortem examination the atrial defect was closed The anterior commissure of the mitral valve was split 0 8 mm and the valve opening was adequate Pulmonary edema and atelectasis were the causes of death in this infant

2 A 34 year old housewife, with a history of congestive manifestations of five years duration, had been at bed rest for two years The heart was more than 80 per cent larger than anticipated She had a large left to right shunt at the atrial level At operation severe mitral stenosis, mild mitral regurgitation, and a large interatrial septal defect were found The mitral valve was fractured and the defect closed She appeared to be improving until the eighth post-operative day, when she expired suddenly Adequate closure of the defect and a good mitral commissurotomy were demonstrated at post mortem examination Microscopic study of the heart muscle showed the presence of acute focal myocardial necrosis Death was probably caused by a ventricular arrhythmia

Uncomplicated ostium secundum defects have usually been closed without the use of elective cardiac arrest In two patients with unusually large secundum defects, potassium citrate was used One recovered uneventfully The second patient, a 37 year old woman, had a bidirectional shunt at the atrial level with pulmonary and systemic blood flows of nearly equal magnitude Her pulmonary artery pressure pre-operatively was 146/60 mm Hg

The defect was closed Post-operatively she did not develop progressive congestive manifestations as we feared She complained of paroxysmal bouts of air hunger, and during these episodes became mildly cyanotic On the fifth post-operative day, she had a convulsive seizure and died Her atrial defect was 4 3 cm in diameter No other defect was present Microscopic study of the lungs showed medial hypertrophy of the small pulmonary arterioles with intimal proliferation to the point of total occlusion in many areas Her pulmonary vascular disease was irreversible

Interatrial Septal Defect with Anomalous Pulmonary Veins

The diagnosis of anomalous pulmonary venous drainage to the right atrium from the right lung was established by pre operative study in a 12-year-old boy His interatrial septal defect was not demonstrated pre-operatively

At operation the right upper and middle lobe pulmonary veins drained into the right atrium posterior to the superior vena caval orifice A very high interatrial defect was found in close proximity to the anomalous vein orifices Repair of the defect was accomplished by suture of the right atrial wall into the defect so that the pulmonary veins were directed into the left atrium

Four hours after operation, he developed acute pulmonary edema and it was feared that thrombosis of the involved pulmonary veins had occurred He died two hours later

Post mortem examination demonstrated that the pulmonary veins were patent Microscopic study showed severe acute focal myocardial necrosis The most severe lesions were in the sub-endocardial area of the left ventricle The cause of death was acute left ventricular failure

Valvular Pulmonic Stenosis with Intact Septa

Since ventriculotomy is not required, elective cardiac arrest is usually not used for these patients Occasionally, however, it may be helpful

1 A 30 year old woman with congestive heart failure and more than 50 per cent cardiac enlargement due to pulmonic stenosis had severe tricuspid regurgitation as a complicating lesion Her pulmonary valve was opened by the usual supra-valvular

approach Her heart was arrested and her tricuspid insufficiency was corrected by direct suture of one commissure through a right atrial cardiotomy She made an excellent recovery

Valvular Pulmonic Stenosis with Interatrial Septal Defect

Elective cardiac arrest has been used in two patients with this combination of defects though it is usually not required

Both patients made uneventful recoveries and are believed to be normal

Infundibular Pulmonic Stenosis with Intact Septa

This lesion is encountered rarely A pre-operative diagnosis of Ebstein's malformation of the tricuspid valve was made in a 42-year-old woman with congestive manifestations of 12 years' duration She was found to have an intact ventricular septum with hypertrophied moderator bands extending across the inflow tract of the right ventricle The pulmonary valve was normal The obstructing bands, having the appearance of anomalous papillary muscles, were excised The patient recovered, but time for adequate evaluation of the ultimate has not yet passed

Aortic Stenosis

For several years the supra-valvular approach to mechanically severe aortic stenosis had been used, without resorting to the use of a pump oxygenator or elective cardiac arrest Surgical evaluation and correction of these lesions was attempted on the basis of palpation of the valve from above, and left a great deal to be desired It was anticipated that the use of a pump oxygenator and elective cardiac arrest would permit a much more definitive surgical approach to this lesion under direct vision

Congenital Aortic Stenosis

Two patients, aged 11 and 18 years, have had aortic valvulotomy for congenital aortic stenosis Excellent visualization of the valves was obtained Satisfactory valvulotomies were performed without the production of aortic regurgitation, and they have made uneventful recoveries

Rheumatic Aortic Stenosis

Rheumatic aortic stenosis has been approached on five occasions

1 The first patient was a 35 year old woman with severe aortic stenosis who had been in congestive failure There was no history of angina pectoris The posterior commissure was incised to the valve ring A second incision was made through the anterior cusp, which was not exactly in line with the adjacent commissure One hour after operation, signs of severe aortic regurgitation appeared with a fall in diastolic pressure to zero She died five hours later in pulmonary edema Post mortem examination revealed aortic regurgitation due to incision of the anterior valve cusp There was also far advanced coronary artery atherosclerosis

2 A 31 year old man recently developed congestive manifestations due to calcific aortic stenosis At operation two of the commissures were precisely incised During the procedure the incision in the aorta extended downward toward the valve ring close to the orifice of the right coronary artery The aorta was closed, but when the aortic clamp was removed to perfuse the coronary arteries, it was not possible to re-establish an effective heart beat Post mortem examination revealed that a suture used in closing the aortic incision obstructed the right coronary artery

3 A 53 year old man had syncopal attacks, severe angina pectoris, calcific aortic stenosis, and generalized arteriosclerosis At operation the left subclavian artery was

used for arterial cannulation Early in the period of cardiac arrest, he suffered a dissection of the aorta from the left subclavian artery extending proximally to within 2 cm of the valve ring and distally down the thoracic aorta for a distance of 17 cm where it terminated in rupture back into the aorta The valvulotomy was completed hurriedly under stress A normal heart rhythm was re-established He died suddenly on the third day after operation after all vital signs had stabilized Autopsy showed no evidence of bleeding from the dissecting aneurysm The valvulotomy was inadequate There was no evidence of myocardial infarction, but extensive atherosclerotic changes were present in all major branches of the coronary arteries A ventricular arrhythmia is believed to have been the immediate cause of death

4 A 41 year old man with severe angina pectoris of two months duration had calcific aortic stenosis An aortic valvulotomy was performed without difficulty On the second post-operative day, he suddenly developed pallor, became dyspneic, and died within 30 seconds Post mortem examination revealed an adequate valvulotomy Coronary atherosclerosis was present involving the proximal branches of all vessels with 30 per cent to 50 per cent occlusion Death was due to cardiac arrhythmia

5 A 58 year old woman had repeated syncopal attacks due to calcific aortic stenosis She recovered from operation without incident She has had no more syncopal attacks in the seven months since operation and has shown an excellent improvement in activity tolerance

It is widely accepted that angina pectoris occurs as a result of severe aortic stenosis When this lesion is present, and evidence of previous myocardial infarction is absent, we have been hopeful that correction of the valve lesion would result in improvement From the above, it is evident that very severe arteriosclerotic heart disease may co-exist with aortic stenosis, and that angina in these patients may be due to this, rather than the valve lesion Better diagnostic methods for defining the status of the coronary circulation in such patients are essential to the solution of this problem

Mitral Regurgitation

Ruptured Chordae Tendineae

1 A 54 year old man had never experienced major rheumatic manifestations A heart murmur was known to be present since puberty and congestive manifestations had been evident for two years Fluoroscopy demonstrated generalized cardiac enlargement and pulsations were seen in the pulmonary arteries Heart catheterization showed a small left to right shunt at the ventricular level Pulmonary artery pressure was 96/41 mm Hg A persisting left superior vena cava draining into the coronary sinus was demonstrated as an incidental finding Operation was performed for correction of an interventricular septal defect Exposure of the heart revealed a palpable thrill over the left atrium characteristic of mitral regurgitation Direct inspection of the valve, through a left atrial cardiotomy, showed chordae tendineae of the medial valve cusp were ruptured An elliptical Ivalon prosthesis was sutured around the mitral valve annulus over the medical commissure Since operation, in October of 1956, congestive manifestations have cleared His heart size has reduced from 17 2 cm to a trans-cardiac diameter of 14 5 cm

Rheumatic Mitral Regurgitation

The above experience, in addition to effective secondary operation on the cleft antero-medial cusp, described under interatrial septal defects, led to the hope that some patients with rheumatic mitral regurgitation might also be benefited

Two attempts to correct rheumatic regurgitation were begun Both patients were lost on the operating table due to dissecting aneurysm of the aorta from the site of faulty arterial cannulation, so that this problem remains untested in our experience The first patient was cannulated from the left subclavian artery In the second, the common femoral artery was used

In perfusing adults, especially older patients in whom arteriosclerotic changes may be anticipated, it would appear wise to divide inflow from the pump, and use two arterial cannulations instead of the customary one The peripheral vessels available cannot withstand the mechanical stress imposed by high velocity flows above 3,000 cc per minute, which are required for adequate perfusion

"Corrected" Transposition of the Great Vessels

Perhaps a more practical term to describe this fortunately uncommon anomaly would be "Transposition of the Vascular Pedicle"

Although the basic course of the circulation is normal, the aorta within the pericardium lies to the left and slightly anterior to the pulmonary artery trunk, giving the vascular pedicle an external appearance like that seen in transposition of the great vessels

Two such patients have been operated upon The pre-operative diagnosis in the first was interventricular septal defect He proved to have a single ventricle which could not be effectively closed, and died immediately after surgery

The second patient was thought to have infundibular pulmonic stenosis and an interventricular septal defect At operation a large defect in the membranous portion of the ventricular septum was found, in addition to two smaller defects in the muscular portion of the septum The pulmonary valve ring was a tiny hypoplastic structure above a grossly narrowed, cone like, right ventricular outflow tract The ventricular defects were closed, but the tiny pulmonary valve ring could not be adequately corrected The child died four hours after operation

Neither of these patients was a suitable candidate for surgical correction since both presented anatomic problems that could not be effectively modified

Pulmonary Hypertension

A 24-year-old woman gave a history of severe dyspnea and syncopal attacks which began to occur at the age of 20 after the delivery of her second child She recalled no rheumatic symptoms She developed progressively severe congestive manifestations and cyanosis during the preceding six months Physical examination revealed a Grade IV systolic bruit with an easily palpable thrill loudest at the left sternal border Cardiac catheterization revealed no evidence of an intra-cardiac shunt Pulmonary artery pressure was 136/74 mm Hg and femoral artery pressure was 114/70 mm Hg

The barium filled esophagus showed abnormal displacement posteriorly and to the left at the level of the left atrium It was finally decided to explore her in the hope of finding a tumor in the left atrium

At operation, there were no valve lesions No tumor was found The septa were intact She died three hours after operation Post mortem examination revealed very severe pulmonary arteriolar disease In retrospect, it is probable that she had amniotic embolization at the time of

delivery, and after recovering from the acute insult, went on to develop chronic cor pulmonale

Transposition of the Great Vessels

Correction of transposition of the great vessels, using the technique postulated by Albert, was attempted in three patients, aged two months, two years, and nine years The posterior aspect of the atrial septum is opened and displaced to the left, permitting pulmonary venous drainage to the right atrium Vena caval flow is directed into the left atrium by the use of an appropriate prosthesis In two patients, this objective was attained In the third, the atrial septum was not displaced far enough to the left to transpose venous return from the left lung In all three, a normal sinus rhythm was restored, but all died within four hours of operation with overwhelming pulmonary congestive changes and anoxia Further attempts in this direction have been abandoned

A-V Heart Block

Before actual clinical trial of elective cardiac arrest, it was feared by some that its use might increase the incidence of complete A-V heart block after open cardiotomy This is known to carry an ominous prognosis, and has been associated with sudden death in post-operative patients weeks or months following surgery This fear has not materialized in practical experience It has been seen in nine of the entire group (11 2 per cent) and transiently in two cases (2 5 per cent) of the survivors Of those who died, one with a single ventricle had complete A-V block before operation, one was a seven pound infant with two interventricular defects, one had unrecognized fibroelastosis in addition to an interventricular septal defect, and another proved to have a single ventricular chamber These, basically inoperable mechanical problems, accounted for four (44 4 per cent) of the nine patients A-V block occurred in two patients with ostium primum defects of the interatrial septum with mitral regurgitation, who were made worse by closure of the septal defect without correction of the valve lesion In one of these it disappeared after a second operation corrected the valve It was seen in two other patients with infundibular pulmonic stenosis and large interventricular septal defects, both of whom died after extensive infundibular resection The remaining instance occurred in a patient with interventricular septal defect who showed unexplained low grade fever for 13 weeks after operation In this patient, it finally disappeared 4 months post-operatively

From the above it would appear that A-V block is associated with pre-existing myocardial disease, surgical injury to the myocardium, or the presence of mechanical lesions which are too severe to be compatible with maintenance of an effective circulation Certainly the use of elective cardiac arrest does not contribute to its occurrence

Conclusions

From the experience described above it is believed the following conclusions may be drawn

1 The use of potassium citrate in the production of elective cardiac arrest for open heart surgery is a routinely applicable procedure, which is completely reversible under the conditions described It increases surgical efficiency without adding hazard to the patient In no instance has its use been responsible for fatality in this series

2 The high mortality rate encountered is a reflection of a combination of factors which include

a Errors in diagnosis
b Errors in judgment in the selection of patients
c Failures in immediate post-operative care, particularly with regard to atraumatic maintenance of adequate ventilatory function in infants and small children
d Surgical errors preventable in view of previous experience
e Surgical errors inevitable at present due to lack of a precise enough understanding of extremely complex and infinitely varied intracardiac pathologic anatomy
f Incomplete solution of the problems involved in total artificial perfusion

The writer is not qualified to define potential improvements in the latter three categories, but in humility born of bitter and occasionally enlightening experience the following statements may be made with regard to diagnosis and selection of patients for surgery

We are passing through the last phases of an era in which the diagnostic appraisal of complex intra-cardiac lesion was based on clinical findings supplemented by physiologic measurements which permitted "diagnosis" on the basis of deduction and reason These things are not depreciated, and will continue to be of utmost importance, but they *are not* adequate to meet the present demands of practical intra-cardiac surgery They must be supplemented by methods that define intra-cardiac structure in motion with at least the precision the pathologist is able to accomplish with the dead heart in his hand Recent developments in x-ray technique, particularly in the field of image amplification combined with high speed motion picture photography, applied to study of the central circulation, appear to constitute at least a forward step in that direction[5] There is reason to hope that further technical improvements in this field, combined with meticulous correlation of pre-operative, surgical, and post mortem findings will make possible a close approach to the ideal of absolutely precise anatomic diagnosis supplemented by routinely dependable evaluation of functional capacity

If these goals can be attained, the problem of selection of patients for surgery will take care of itself, as the limitations and scope of open heart surgery are further defined by increasing surgical experience

SUMMARY

Elective cardiac arrest, accomplished by perfusion of potassium citrate solution into the coronary circulation, has made possible excellent surgical exposure of intra-cardiac structures during open cardiotomy in 80 patients

with a wide variety of congenital and acquired lesions The cardioplegic effect of potassium was reversed by perfusing the coronary arteries with oxygenated blood In no instance was death or surgical failure attributable to the use of cardiac arrest

Forty-five patients have survived Reasons for death have been stated within the limits of our present knowledge The post-operative status of surviving patients has been evaluated on the basis of clinical findings and, when possible, by heart catheterization and cinecardioangiography six to 14 months after operation

Anatomic correction with restoration of normal function may be anticipated in patients with atrial or ventricular septal defects, provided complete absence of the septum is not encountered

Severe pulmonary hypertension is not a contra-indication to closure of septal defects, if there is a large left to right shunt with increased pulmonary flow

In patients with Tetralogy of Fallot, inadequate closure of the ventricular septal defect has been found in most instances when a prosthesis has not been incorporated into the defect These patients have shown clear-cut evidence of functional improvement, with increased pulmonary blood flow and relief of arterial hypoxemia, but anatomic correction and restoration of normal cardiovascular dynamics has usually not been obtained

Experience with this small group of patients emphasizes the need for further refinements in diagnosis, surgical technique, artificial perfusion and post-operative management before the ultimate potential of open heart surgery may be fully realized

RESUMEN

La perfusión de una solución de citrato de potasio ha hecho posible obtener a voluntad la detención del corazón para lograr una exposicion quirúrgica excelente de las estructuras intracardiacas durante la cardiotomía en 80 enfermos con una variedad de afecciones congénitas o adquiridas El efecto cardioplégico del potasio se contrarrestó por la perfusión de las coronarias con sangre oxigenada En ningúan caso fué de atribuirse la muerte a la detención cardiaca provocada o la insuficiencia cardiaca pudo atribuirse a esa misma causa

Han sobrevivido 45 enfermos Las causas de defunción se establecieron dentro de los límites de los conocimientos actuales El estado post-operatorio de los enfermos sobrevivientes se ha estimado basándose en los hallazgos clínicos y cuando fué posible, por la cateterización cardiaca y por cineangiocardiografía de 4 a 14 meses después de la operación

La corrección anatómica con restauración de la función normal puede preverse en los enfermos con defectos atriales o septo-ventriculares siempre que no se trate de ausencia completa del septum

La hipertensión pulmonar severa no es una contraindicación a la oclusión de los defectos septales si hay un amplio paso de izquierda a derecha con aumento del flujo sanguíneo pulmonar

En los enfermos con tetralogía de Fallot el cierre inadecuado del defecto del tabique ventricular se ha encontrado en la mayoría de los casos cuando una prótesis no se ha incorporado dentro del defecto Estos enfermos han mostrado definida evidencia de mejoría funcional con aumento del flujo sanguíneo pulmonar y alivio de hipoxemia arterial, pero la corrección anatómica y la recuperación hospitalización prolongada pueden ser evitadas por la excisión cuando son asintomáticas, inactivas y esa excisión da una morbilidad y mortalidad mínimas

Hubo complicaciones de importancia en 5 casos pero solo uno trajo como consecuencia el dejar de volver al servicio activo

Hubo una muerte debida a shock postoperatorio de causa indeterminada Setenta y nueve por ciento regresaron a servicio activo y como los cambios de actitud recientes consideran la necesidad de tratamiento de largo plazo de la tuberculosis se cree que más del 90 por ciento se rehabilitarán para continuar el servicio naval activo

RESUME

L'arrêt cardiaque électif par perfusion d'une solution de citrate de potassium dans la circulation coronarienne a rendu possible une excellente mise en évidence chirurgicale des formations intra-cardiaques pendant une cardiotomie à coeur ouvert chez 80 malades atteints d'une gamme étendue de lésions congénitales ou acquises L'effet cardioplégique du potassium fut combattu par la perfusion dans les artères coronariennes de sang oxygéné En aucun cas la mort ou l'échec chirurgical ne put être attribué à l'emploi de l'arrêt cardiaque

45 malades survécurent La cause des décès a été déterminée dans les limites de nos connaissances actuelles La condition post-opératoire des malades ayant survécu a été évaluée sur la base des constatations cliniques, et quand ce fut possible, par cathétérisme cardiaque et cinécardioangiographie, 6 à 14 mois après l'opération

On peut compter sur une correction anatomique avec restauration de la fonction normale chez les malades atteints d'imperfection de la paroi de l'oreillette ou du ventricule, à condition qu'on ne rencontre pas une absence complète du septum

Une hypertension pulmonaire grave n'est pas une contreindication à la fermeture des imperfections de la paroi, s'il y a un shunt important de gauche à droite, avec débit pulmonaire augmenté

Chez les malades atteints de tétralogie de Fallot, dans la plupart des cas, on ne put obtenir une occlusion parfaite de l'anomalie du septum ventriculaire à moins de faire appel à une correction avec prothèse Ces malades ont montré la preuve nette d'une amélioration fonctionnelle, avec augmentation du débit sanguin pulmonaire, et soulagement de l'hypoxémie artérielle, mais la correction anatomique et la restauration de la dynamique cardiovasculaire normale n'a généralement pas été obtenue

L'expérience pratiquée sur ce petit groupe de malades souligne la nécessité de perfectionnements ultérieurs dans le diagnostic, la technique chi-

rurgicale, la perfusion artificielle et la conduite post-opératoire, avant que les possibilités de la chirurgie à coeur ouvert ne soient complètement obtenues

ZUSAMMENFASSUNG

Elective Herzstillstand, begleitet von Durchstromung des Coronarkreislaufes mit Kalium-Citrat-Losung ermoglichte ausgezeichnete chirurgische Darstellung von intracardialen Strukturen wahrend offener Cardiotomie bei 80 Kranken mit einer betrachtlichen Vielzahl angeborener und erworbener Veranderungen Die Herzlahmende Wirkung von Kalium wurde aufgehoben durch Durchstromung der Coronararterien mit Sauerstoffgesattigtem Blut In seinem Fall war der Tod oder chirurgisches Versagen der Anwendung von Herzstillstand zuzuschreiben

Es uberlebten 45 Patienten Die Todesursachen wurden dargelegt innerhalb der Grenzen unserer heutigen Kenntnis Der postoperative Status der uberlebenden Patienten wurde auf der Grundlage der klinischen Befunde ausgewertet, sowie, wenn moglich, durch Herzkatheterisierung und Cineangiocardiografie 6-14 Monate nach der Operation

Eine anatomische Korrektur mit Wiederherstellung der normalen Funktion kann erwartet werden bei Patienten mit Vorhof- oder Kammer-Septum-Defekten, sofern nicht volliges Fehlen des Septums angetroffen wird

Schwerer *pulmonaler* Hochdruck ist keine Kontraindikation fur den Verschluss von Septum-Defekten, wenn ein erheblicher Links-Rechts-Shunt besteht mit vermehrter *pulmonaler* Durchstromung

Bei Kranken mit Fallot'scher Tetralogie ergab sich in den meisten Fallen ein unzureichender Verschluss des Ventrikel-Septum-Defektes, wenn nicht eine Prothese in den Defekt eingesetzt worden war Diese Kranken zeigten eindeutige Anhaltspunkte fur funktionelle Besserung mit vermehrter pulmonaler Blutzirkulation und Beseitigung der arteriellen Hypoxaemie, jedoch wurde fur gewohnlich eine anatomische Korrektur und Wiederherstellung der normalen Herz-Kreislauf-Dynamik nicht erreicht

Die Erfahrung an dieser kleinen Patientenzahl unterstreicht das Bedurfnis nach weiteren Verfeinerungen in der Diagnose, der chirurgischen Technik, der kunstlichen Durchstromung und postoperativen Behandlung, ehe das ausserst Mogliche in der Chirurgie des offenen Herzens in vollem Umfang Wirklichkeit werden kann

REFERENCES

1 Melrose, D G, Dreyer, B, Bentall, H H and Baker, J B S "Elective Cardiac Arrest," *Lancet*, 2 21, 1955
2 Kolff, W J, Effler, D B, Groves, L K, Peereboom, G, Aoyama, S and Sones, F M, Jr "Elective Cardiac Arrest by the Melrose Technic Potassium Asystole for Experimental Cardiac Surgery," *Cleve Clin Quart*, 23 98, 1956
3 Effler, D B, Groves, L K, Sones, F M, Jr, Knight, H F, Jr and Kolff, W J "Elective Cardiac Arrest An Adjunct to Open Heart Surgery," *J Thoracic Surg*, in Press
4 Albert, H M "Surgical Correction of Transposition of the Great Vessels," *Am College of Surgeons, Surgical Forum*, 5 74, 1955
5 Sones, F M, Jr "New Tools for Research Heart Catheterization and Selective Cardioangiography," *Modern Medicine Annual*, 1 188, 1957

Experimental Coronary Artery Occlusion Ventricular Fibrillation and Survival as Affected by Selected Drugs and Ionic Alterations*, **

WILLIAM T WILLIAMS, M D,*** ALBERT L MEENA, M D,
M DON TURNER, Ph D and JAMES D HARDY, M D
Jackson, Mississippi

The effect of drugs and ions upon the normal heart and upon isolated myocardium has been thoroughly investigated and adequately documented Increased interest in the application of these substances in a manner which approaches the abnormal clinical situation—that is, following coronary artery occlusion and in various arrythmias—has been demonstrated during the past few years The stimulus for this recent investigative trend has come primarily from three sources (1) Fibrillation following coronary artery occlusion and the efforts to devise means of permanently increasing collateral blood supply to the myocardium, (2) Cardiac arrest or ventricular fibrillation during surgery, and (3) Ventricular fibrillation during hypothermia

This report concerns experimental myocardial ischemia produced by acute coronary artery occlusion, the influence of drugs and inorganic ions on survival rates and early fibrillation and the influence on certain ions upon other ions

Materials and Methods

Adult mongrel dogs were used as the experimental animals Following anesthetization with intravenous nembutal, endotracheal intubation was accomplished and the chest opened by an incision in the fourth inter-space The left coronary, circumflex coronary, and left anterior descending coronary arteries were carefully demonstrated A heavy silk ligature was placed beneath the anterior descending branch immediately adjacent to its origin The loose ligature was threaded through a small plastic tube which was anchored to the pericardium at one end and brought out through the chest wall at the other end Following closure of the chest wall, the ligature ends and plastic tube were placed subcutaneously, the animal was given penicillin and returned to his cage

The following day the animal was again anesthetized, control electrocardiograms obtained, and control blood samples drawn for plasma pH, potassium, sodium, chloride, calcium and carbon dioxide tension The animals were then divided into the following groups depending upon the drug or ion which was administered (1) Control, one day postopera-

*From the Surgical Experimental Laboratory and the Department of Surgery, University of Mississippi School of Medicine, Supported by U S Public Health Service Grant No H-2806 and Mississippi Heart Association Grant

*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

**Public Health Research Fellow of the National Heart Institute Presently at Dunedin, Florida

tive—10 dogs—no infusion (2) Control, 20 days postoperative—three dogs—no infusion (3) Acidosis—five dogs—100-140mEq hydrochloric acid in 400 cc water (4) Alkalosis—five dogs—140-150mEq sodium bicarbonate in 400 cc distilled water (5) Hyperkalemia—five dogs—30-45mEq potassium chloride in 400 cc. distilled water (6) Hypercalcemia—five dogs—1 gm calcium chloride in 400 cc 5 per cent dextrose in distilled water (7) Excess sodium chloride—five dogs—4½ gm sodium chloride in 500 cc distilled water (8) Procaine—five dogs—500 mgm "Novacaine" in 400 cc 5 per cent dextrose (9) Papaverine —five dogs—30 mgm papaverine intravenously (10) Quinidine—five dogs—100 mgm quinidine intravenously Immediately following the infusion, electrocardiograms were again obtained and blood samples drawn for the determinations listed above The ligature was tightened, completely occluding the left anterior descending coronary artery and electrocardiograms were obtained at frequent intervals to one hour postocclusion If the animal still lived at the end of this period he was returned to his cage without further care Early fibrillation as used in this communication denotes fibrillation occurring during the sixty minutes following coronary artery occlusion Mortality was determined at the end of the first 24 postoperative hours pH was determined on the Beckman model G pH meter Calcium was determined by titration with EDTA Sodium and potassium were analyzed on the Beckman direct reading flame photometer Chlorides were determined by a modification of the Volhard method Carbon dioxide tension was measured by the Van Slyke manometric technique

Results

(1) Control The mortality following ligation of the left anterior descending coronary artery has been reported on large series of dogs by others so that we considered it necessary to use only 10 animals occluded on the first postoperative day The mortality in these 10 dogs was 80 per cent with 30 per cent of the deaths due to early fibrillation which occurred during the first 12 minutes following ligation

(2) Control, 20 days postoperative Of passing interest is the fact that this experiment was designed originally to allow the animal to recover from thoracotomy and dissection around the coronary artery We soon found that if ligation were delayed following pericardotomy we failed to achieve any mortality This point is borne out in three cases in which ligation was delayed for 20 days after thoracotomy In this group there was no mortality and in two of the three animals there was no change in the electrocardiogram pre and postocclusion

(3) Acidosis Hydrochloric acid in the amounts used in this study produced an acidosis with a mean pH of 7 22 as opposed to a mean control pH of 7 37 This group of five animals suffered an 80 per cent mortality and 40 per cent fibrillation rate

(4) Alkalosis The mean pH was elevated to 7 62 from a mean control of 7 37 by the infusion of sodium bicarbonate The mortality rate was 80 per cent and fibrillation rate 60 per cent

(5) Hyperkalıemıa A moıtalıty ıate of 60 peı cent and a fibııllatıon ıate of 60 per cent ıesulted when the mean potassıum was elevated to 6 24 mEq peı lıteı fıom a mean contıol of 3 7 mEq per lıteı by ınfusıon of potassıum chloııde

(6) Hypeıcalcemıa The ınfusıon of 1 gm of calcıum chloııde elevated the seıum calcıum fıom a mean control of 5 mEq peı lıteı to 7 7 mEq peı lıteı Mortalıty 80 per cent, fıbrıllatıon 60 per cent

(7) Excess Sodıum Chloııde Only 500 cc of 0 9 sodıum chloride was ınfused and thıs haıdly repıesents an excess as demonstıated by the mınımum ııse ın sodıum and chloııde However, 100 peı cent mortalıty and 80 peı cent fibııllatıon resulted

(8) Pıocaıne A moıtalıty ıate of 100 per cent and fibııllatıon ıate of 100 per cent ıesulted when 500 mgm of "Novacaıne" was ınfused

(9) Papaverıne The ıntravenous admınıstıatıon of papaveıne, 30 mgm yielded moıtalıty and fibrıllatıon rates of 60 per cent

(10) Quınıdıne A mortalıty of 60 peı cent, and fibııllatıon of 60 peı cent followed the ıntıavenous admınıstratıon of Quınıdıne, 100 mgm

(11) Ions The ınfluence of ınfusıon of ceıtaın ıons and drugs upon the blood level of otheı ıons ıs chaıted ın Figure 1

Dıscussıon

One of the earlıest stımulı foı ınvestıgatıon of ventııcular fibııllatıon aıose as the result of thıs lethal aııythmıa followıng coıonaıy aıtery occlusıon Unfoıtunately, medical attempts at pıeventıng fibııllatıon have met with no success despite the tremendous amount of ınvestigatıve work devoted to the problem Wıggers[1] ın 1940 ın dıscussıng the mechanısm of ventııculaı fibııllatıon followıng coronary occlusıon found that a sıgnıfıcantly smalleı amount of electıic cuıent was requııed to fıbrıllate the heart followıng experımental coıonary occlusıon than noımally He theorızed that spontaneous fıbrıllatıon duıng oı followıng coıonary occlusıon was pıecipıtated because usually ınnocuous ectopic stımulı became of precipıtatıng level foı the hyperırrıtable myocardıum Beck[2] employed the teım "electrıcally unstable heaıt" ın dıscussıng the mechanısm of ventrıculaı fıbrıllatıon He found that 90 peı cent of all the people who dıe of coıonaıy aıtery dısease dıe because the heaıt becomes electrıcally unstable and fibııllates The electrıcally stable heaıt ıs one ın whıch oxygen satuıatıon ıs unifoım thıoughout, and thıs stabılıty peısısts when the oxygen tensıon ıs ıeduced provıded the reductıon ıs unıform thıoughout the myocardıum The heaıt becomes electrıcally unstable and may fibııllate when the oxygen tensıon ıs not unifoım thıoughout the myocaıdıum, that ıs, when an aıea wıth decıeased oxygen tensıon ıs suırounded wıth well-oxygenated myocardıum or vıce veısa If some substance could be gıven whıch would appıecıably decrease the hypeıiııitabılıty of the myocaıdıum and the ıncıdence of fibııllatıon followıng coronaıy occlusıon, substantıal pıogıess would have been achıeved Thıs was one of the clınıcal applıcatıons ın mınd when thıs pıoject was undertaken

The consistent level of coronary artery ligation in any study of mortality following coronary occlusion has been emphasized repeatedly Our control mortality rate of 80 per cent is similar to that of others who have used the same location for coronary occlusion Hahn[1] reported a mortality rate of 70 per cent following ligation of the descending ramus of the left coronary artery Bakst[1] reported a mortality rate of 60 per cent when the same artery was ligated but mentioned that the higher survival rate might have been due to the high incidence of an accessory left anterior descending coronary artery which arose from the circumflex branch of the left coronary artery Vineberg[5] noted a mortality rate of 90 per cent McAllister[4] showed an immediate mortality rate of 70 per cent following ligation of the anterior descending branch in a group of 100 dogs The incidence of early fibrillation is not so widely reported but Beck[2] noticed early fibrillation in 50 per cent of his animals at normothermic temperatures

Because of the nature of this study utilizing various ions and drugs, it was important to determine the incidence of early fibrillation Because

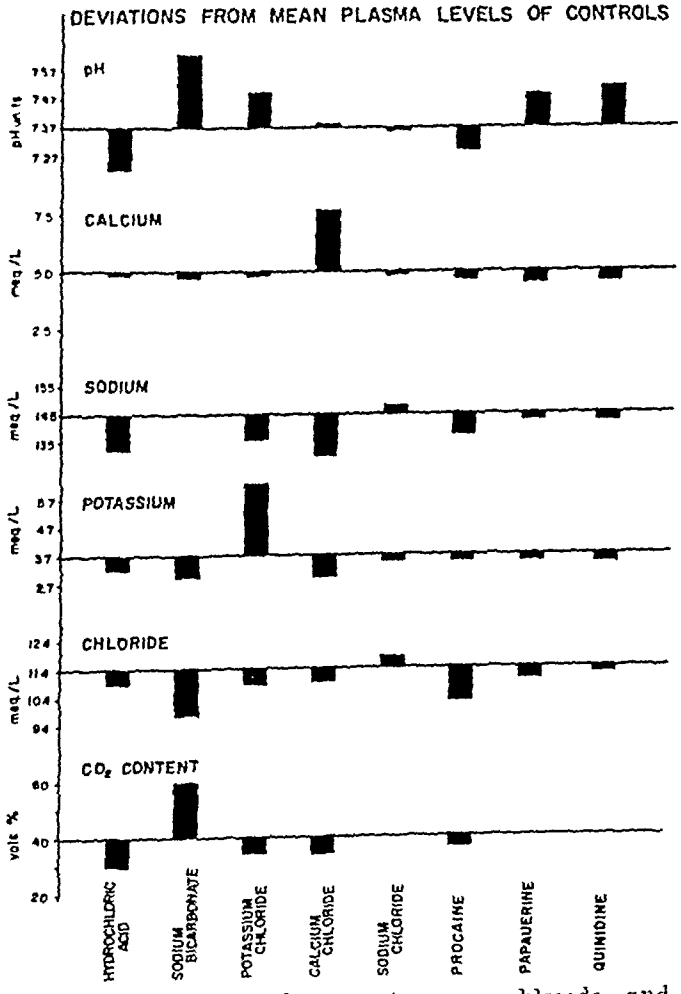


FIGURE 1 Plasma pH, calcium, sodium, potassium, chloride, and CO_2 content as affected by the ions and drugs employed in the study The base line, from which the deviations are charted, represents the mean of the control determinations Because of space considerations, these results are not discussed in the text and form the basis of a separate report

these substances were administered only once immediately before coronary occlusion and were not administered to the surviving animals, a clear picture of the worth of the substance can be drawn from the early fibrillation rates rather than the overall mortality rates when the drug may have lost its effect Our early fibrillation rate of 30 per cent is somewhat lower than that reported by Beck although the ultimate mortality rate is similar

During the past several years efforts have been made along several lines to devise some procedure which would materially and consistently increase collateral blood supply to the myocardium One of the earliest and still one of the relatively most successfully employed is the principle of irritation of the pericardium and myocardium to encourage collateral vessel growth to the myocardium The three animals in this series whose coronary artery ligation was delayed 20 days following pericardotomy come under this category although no deliberate attempt was made to stimulate collateral vessel growth It has been shown previously that simple pericardotomy offers significant protection to the animal when coronary occlusion is delayed for several days In our series, in addition to opening the pericardium, a polyethylene tube and a large silk suture were left within the pericardium for 20 days An additional stimulus for collateral vessel growth may have been bacterial pericarditis resulting from the clean, but not sterile, technique and propagated by the intrapericardial foreign bodies In any event, we were surprised that the collaterals were of sufficient content as to prevent electrocardiographic evidence of coronary occlusion in two of the three animals, in addition to the survival of all three animals in the group This group is of insufficient size to furnish any conclusions and, of course, was not originally designated for that purpose However, it does point out the difficulty in evaluating some of the experimental results of other forms of myocardial vascularization

During the past few years cardiac arrest or ventricular fibrillation occurring during an operation has been the subject of an ever increasing investigative effort During the early years of these studies various anesthetic agents or combinations thereof were thought to be contributing factors toward ventricular fibrillation However, during recent years carbon dioxide retention, acidosis and anoxia have been implicated as the contributing factors With the advent of hypothermia, ventricular fibrillation attained even greater notoriety It was essential that the incidence of ventricular fibrillation be greatly reduced or abolished if hypothermia were to continue in use as a procedure with acceptable risk Few projects have been the subject of such intense investigation as has ventricular fibrillation in hypothermia Certain investigators suggested that ventricular fibrillation might be used as an ideal state during surgery in the heart employing hypothermia and extracorporeal circulation However, the majority of surgeons consider ventricular fibrillation a hazard worthy of avoiding Cahn and Melon[7] reported the use of xylocaine anesthetization of the sinoauricular node as a means of preventing ventricular

fibrillation during hypothermia. Ribeiro, Sideris, and Shumacker[8] have effectively utilized procaine injection of the sino-auricular node. Webb[9] by injecting the auriculoventricular node with procaine, has achieved even greater protection against fibrillation.

While these measures have been successful, investigation along other lines has strongly implicated potassium as the excitatory agent for ventricular fibrillation. Harris[10] et al. injected potassium chloride solutions in varying concentrations into coronary arteries of dogs and noted that the intensity of ectopic ventricular activity depended upon the amount of potassium chloride present. Following coronary ligation, there was a large increase in the potassium content of venous blood from the ischemic area, increasing from a control level of 12.75 mgm. per cent to 24.5 mgm. per cent. The potassium concentration showed a positive correlation with the ectopic activity. In addition, potassium concentration reapproached control levels during the periods that corresponded to the times of disappearance of ectopic activity. At that time potassium content of the infarcted muscle was greatly reduced. Montgomery, Prevedel, and Swan[11] likewise obtained convincing evidence relating potassium and plasma pH to ventricular fibrillation. Hooker[12] found that ventricular fibrillation in the isolated perfused heart could be converted by the addition of potassium to the perfusing medium. Brown and Miller[13] produced ventricular fibrillation in 11 of 15 dogs by a rapid reduction in alveolar carbon dioxide tension following 4 hours of breathing 30 to 40 per cent carbon dioxide.

Our studies suggest that there is no correlation between serum potassium

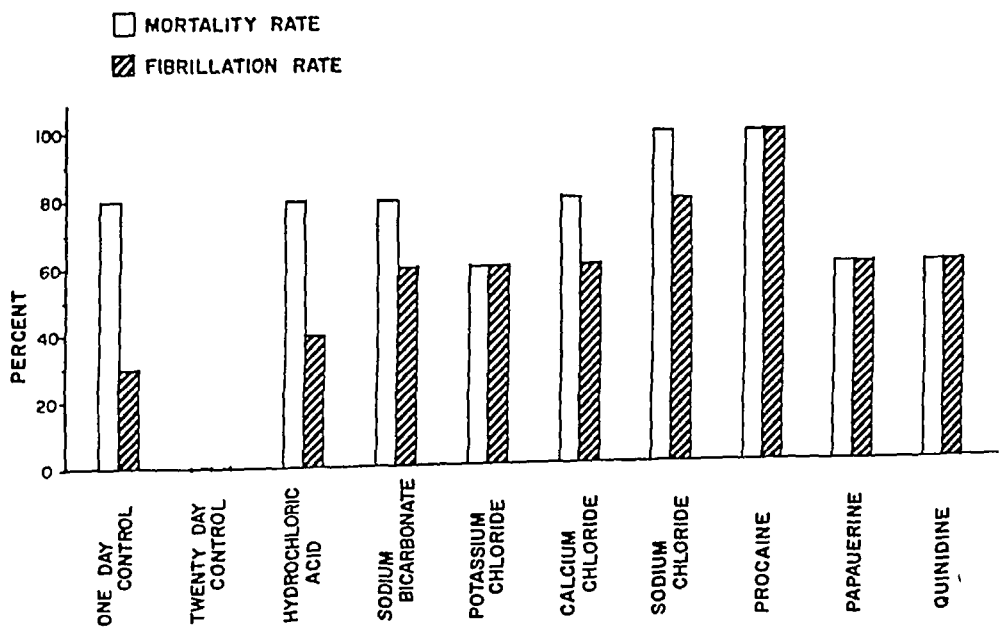


FIGURE 2. Mortality and fibrillation rates of the control and the various ion and drug series.

level and ventricular fibrillation When Figs 1 and 2 are inspected it is noted that when the serum potassium was lowest, as in the sodium bicarbonate and calcium chloride series, a fibrillation rate of 60 per cent occurred When the serum potassium was considerably increased by the infusion of potassium, fibrillation again occurred in 60% of the animals Thus it would appear that if potassium is the excitatory agent for ventricular fibrillation that myocardial potassium is unaffected by plasma concentration and is on a metabolic basis

Grumbach[14] et al, using isolated rabbit hearts, studied ventricular fibrillation as related to calcium and potassium Their results indicated that the initiation of fibrillation was dependent upon the calcium content in the tissue fluid which in turn was determined by the potassium content in the fluid In our studies in which the serum levels of calcium and potassium were considerably increased, the 60 per cent fibrillation rate was the same in each although the ultimate mortality in the hypercalcemia group was slightly higher

Bellet[15] in discussing the possible modes of action of 0 5 molar sodium lactate in preventing or correcting cardiac arrythmias considered that one of the beneficial actions of this solution might be due to the production of alkalosis In this study, employing sodium bicarbonate rather than sodium lactate to obtain a significant alkalosis, the mortality rate following coronary occlusion was the same as the control but the fibrillation rate of 60 per cent was twice the control level Thus, alkalosis as obtained with sodium bicarbonate, does not reduce the fibrillation rate which follows the demanding stimulus of coronary occlusion

Montgomery's[11] observation showed that blood pH influenced the concentration of potassium in the myocardium, demonstrating that with a low pH the heart takes up potassium whereas with a high pH the heart maintains potassium balance In our series the mortality and fibrillation rates in the acidosis group most closely approached the control levels whereas the alkalosis group demonstrated fibrillation rates twice the control levels although the ultimate mortality was the same Again, if potassium is the agent inciting ventricular fibrillation, it would appear that myocardial metabolism of potassium in myocardial ischemia is unaffected by blood pH insofar as decreasing early fibrillation is concerned

The mortality rate of 100 per cent and fibrillation rate of 80 per cent obtained when coronary occlusion followed infusion of 500 cc 0 9 per cent sodium chloride is difficult to explain It can be seen from Figure 1 that the elevation of sodium and chloride were minimal and that the other ions measured were not appreciably changed In addition, the volume of fluid employed in the infusion was similar to that used in the other series

The studies of Long[16] and associates show that the intravenous administration of procaine in normal dogs in increasing dosages produced successively, bundle-branch block, slowing of conduction through the A-V node, ventricular tachycardia, and ultimately ventricular fibrillation

Their studies also suggested that in hearts with muscle damage cardiac changes occurred with therapeutic doses of procaine Van Dongen[17] found that "Novacaine" was active against electrical fibrillation and its after effects and against heterotopic rhythms caused in other ways Wiggers and Wegria,[18] employing cats' hearts and electrical stimulation, concluded that procaine raised the resistance of the ventricles to fibrillation but did not prevent its occurrence In our study, in which coronary ligation rather than electric current was used as a stimulus, intravenous procaine was the most lethal agent used insofar as fibrillation was concerned with a 100 per cent mortality and 100 per cent fibrillation rate resulting

In discussing antifibrillatory drugs, DiPalma and Schultz[19] showed that papaverine raised the threshold for ventricular fibrillation In addition, papaverine intravenously was demonstrated to be a marked coronary dilator which was considered to be one of the reasons for its beneficial action in fibrillation However, it was stated that papaverine might cause ventricular fibrillation in large doses Elek-[20] studied the effects of increasing levels of papaverine on the animal electrocardiograms In addition he demonstrated that the favorable action of papaverine in reversing artificially induced ventricular fibrillation was due to depression of conductivity and irritability and to prolongation of the refractory period of the ventricles In this present series, using 30 mgm of papaverine intravenously, the fibrillation rate was twice the control although the mortality rate was slightly reduced

Hess and Haugaard[21] studied the effect of quinidine on the carbohydrate metabolism of rat heart slices and homogenates In varying concentrations quinidine produced marked inhibition of glucose utilization and oxygen uptake by homogenates In some of the older medical literature[22-24] quinidine was believed to be beneficial in ventricular tachycardia following coronary thrombosis Moissette,[24] studying the action of quinidine following occlusion of the descending branch of the coronary artery concluded that quinidine did not prevent ventricular fibrillation but on the contrary often favored it in the presence of coronary occlusion Smith,[25] investigating the action of quinidine by a method similar to the one employed in this study, concluded that the dog's myocardium was rendered more susceptible to the development of cardiac irregularities by quinidine sulfate The mortality rate in his series following occlusion of the left circumflex coronary artery was reduced from 75 to 55 per cent when large doses of quinidine were administered intravenously The mortality and fibrillation rate of 60 per cent in our quinidine series would suggest that it favors the development of ventricular fibrillation

SUMMARY

1 The effect of selected drugs and various inorganic ions on ventricular fibrillation and mortality following experimental coronary artery occlusion has been investigated

2 Control mortality of 80 per cent and early fibrillation of 30 per cent

was obtained following ligation of the left anterior descending coronary artery immediately at its origin

3 When coronary occlusion was delayed for 20 days post-pericardotomy in three animals there was no mortality and two of the three animals failed to demonstrate any change in the pre and postocclusion electrocardiogram

4 Mortality of 80 per cent and fibrillation of 40 per cent resulted when acidosis was produced by hydrochloric acid

5 Mortality of 80 per cent and fibrillation of 60 per cent resulted when alkalosis was produced by the infusion of sodium bicarbonate

6 A mortality rate of 60 per cent and a fibrillation rate of 60 per cent resulted when hyperkalemia was produced

7 Hypercalcemia produced a mortality of 80 per cent and fibrillation of 60 per cent

8 Following the infusion of a relatively small amount of sodium chloride an unexpected 100 per cent mortality and 80 per cent fibrillation rate resulted

9 A mortality rate of 100 per cent and a fibrillation rate of 100 per cent followed the infusion of procaine

10 The intravenous administration of papaverine produced mortality and fibrillation rates of 60 per cent

11 Quinidine administered intravenously yielded a mortality rate of 60 per cent and fibrillation rate of 60 per cent

12 The influence of infusion of certain ions and drugs upon the concentration of other ions was determined

13 It would appear from this study that if potassium is the excitatory agent for ventricular fibrillation that myocardial potassium in ischemia is unaffected by the plasma concentration of potassium and is on a metabolic basis

14 If potassium is the agent inciting ventricular fibrillation it would appear from this study that myocardial metabolism of potassium in myocardial ischemia is unaffected by blood pH insofar as decreasing early fibrillation is concerned

15 None of the drugs or ions employed in this study showed any beneficial effect on reducing mortality or ventricular fibrillation following coronary artery occlusion

We gratefully acknowledge the electrocardiographic interpretation of Dr Thomas M Blake

RESUMEN

1 Se investigó el efecto de drogas seleccionadas, y de varios iones inorgánicos sobre la fibrilación ventricular así como sobre la mortalidad después de la oclusión coronaria experimental

2 Se obtuvo el control de la mortalidad en el 80 por ciento y fibrilación temprana en el 30 por ciento después de ligadura de arteria coronaria descendente izquierda inmediatamente en su origen

3 Cuando la oclusión coronaria fué retardada por 20 días después de la pericardiotomía en tres animales no hubo mortalidad y en dos de

los tres animales no se observó cambio alguno en el electrocardiograma antes y después de la oclusión.

4 Resultó una mortalidad de 80 por ciento y fibrilación de 40 por ciento cuando hubo acidosis provocada por ácido clorhídrico

5 Una mortalidad de 80 por ciento y fibrilación de 60 por ciento resultó cuando se produjo alcalosis por infusion de bicarbonato de sodio

6 Cuando se provocó hiperkalemia hubo una mortalidad de 60 por ciento y fibrilación de 60 por ciento

7 La hipercalcemia produjo una mortalidad de 80 por ciento y fibrilación de 60 por ciento

8 Después de una infusión de una cantidad relativamente pequeña de cloruro de sodio, resulto una inesperada mortalidad de 100 por ciento y fibrilación de 80 por ciento

9 La mortalidad fué de 100 por ciento y la fibrilación de 100 por ciento, después de la infusión de procaina

10 La administración intravenosa de papaverina produjo mortalidad y fibrilación en 60 por ciento

11 La quinidina intravenosa dió una mortalidad de 60 por ciento y fibrilación de 60 por ciento

12 Se determinó la influencia de la infusión de ciertos iones y drogas sobre la concentración de otros iones

13 Parecería según este estudio que si el potasio es el agente excitador para la fibrilación ventricular, el potasio miocárdico en la isquemia no es afectado por la concentración del potasio en el plasma como lo es sobre base metabólica

14 Si el potasio es el provocador de fibrilación ventricular parecería según este estudio, que el metabolismo miocárdico del potasio en la isquemia del miocardio no es afectado por el pH sanguíneo en lo referente al decrecimiento de la fibrilación temprana

15 Ninguna de las drogas o iones empleados en este estudio mostró efecto benéfico alguno para reducir la mortalidad o la fibrilación ventricular después de la oclusión coronaria

RESUME

1 L'auteur a examiné l'effet de médications choisies et de différents ions inorganiques sur la fibrillation ventriculaire et sur la mortalité consécutive à l'occlusion expérimentale de l'artère coronaire

2 Il obtint de ramener le taux de mortalité à 80% et la fibrillation précoce à 30% après ligature de l'artère coronaire descendante antérieure gauche, immédiatement à son origine

3 Lorsque l'occlusion coronarienne ne suivint que 20 jours après la péricardotomie chez trois animaux, il n'y eut aucune mortalité, et chez deux des trois animaux on ne put mettre en évidence la moindre altération de l'électrocardiogramme avant et après l'occlusion

4 Un taux de mortalité à 80% et 40% de fibrillation furent obtenus quand on créa une acidose par acide chlorhydrique

5 Un taux de mortalité de 80% et de 60% de fibrillation fut obtenu lorsque on produisit une alcalose par injection de bicarbonate de soude

6 Un taux de mortalité de 60% et un taux de fibrillation de 60% furent obtenus par l'hyperkaliemie

7 L'hypercalcémie produisit une mortalité à 80% et 60% de fibrillation

8 Après injection d'une quantité relativement faible de chlorure de sodium, un taux de mortalité inattendu à 100% et 80% de fibrillation se produisirent

9 Un taux de mortalité de 100% et de 100% de fibrillation suivirent l'injection de procaine

10 L'injection intraveineuse de papaverine produisit des taux de mortalité et de fibrillation de 60%

11 La quinidine administrée par voie intraveineuse provoqua un taux de mortalité de 60% et un taux de fibrillation de 60%

12 L'auteur détermina l'influence de l'injection de certains ions et médications sur la concentration des autres ions

13 D'après cette étude, il apparaîtrait que le potassium est l'agent excitateur de la fibrillation ventriculaire, que le potassium du myocarde dans l'ischémie n'est pas affecté par la concentration plasmatique de potassium et l'est sur la base métabolique

14 Si le potassium est l'agent provocateur de la fibrillation ventriculaire, il apparaîtrait d'après cette étude, que le métabolisme myocardique du potassium dans l'ischémie myocardique n'est pas affecté par le pH sanguin, au moins autant que le diminution de la fibrillation précoce est intéressée

15 Aucune des médications ou des ions utilisés dans cette étude ne montra un effet bénéfique sur la réduction de la mortalité ou de la fibrillation ventriculaire après occlusion de l'artère coronaire

ZUSAMMENFASSUNG

1 Es wurden die Wirkungen von ausgewahlten Arzneimitteln und verschiedenen anorganischen Jonen bei Kammerflimmern und Tod nach experimentellen Coronararterienverschluss untersucht

2 Eine Kontroll-Mortalitat von 80% und ein fruhzeitiges Flimmern von 30% wurden erzielt nach der Ligatur des vorderen absteigenden coronararterienastes unmittelbar an seinem Abgang

3 Wurde der Coronarverschluss bei 3 Tieren aufgeschoben um 20 Tage nach der Pericardotomie, so gab es keine Sterblichkeit und bei² von den 3 Tieren war es nicht moglich, irgendeine Veranderung im EKG vor und nach dem Gefassverschluss nachzuweisen

4 Eine Mortalitat von 80% und ein Flimmern in 40% traten ein, wenn eine Acidose durch Salzsaure erzeugt wurde

5 Eine Mortalitat von 80% und Flimmern in 60% traten ein, wenn eine Alkalose erzeugt wurde durch die Infussion von Natrium-Bicarbonat

6 Eine Mortalitat von 60% und Flimmern in 60% traten ein, wenn eine Hyperkalaemie erzeugt wurde

7 Hypercalcaemie fuhrte zu einer Mortalitat von 80% und Flimmern in 60%

8 Im Anschluss an die Infussion einer relativ geringen Menge von Kochsalz ergab sich eine nicht erwartete Mortalitat von 100% und Flimmern in 80%

9 Eine Mortalitatsziffer von 100% und Flimmern in 100% folgte der Infussion von Novocain

10 Die intravenose Verabfolgung von Papaverin fuhrte zu Mortalitats- und Flimmer-Raten von 60%

11 Quinidin intravenos zugefuhrte erbrachte eine Mortalitat von 60% und Flimmern in 60%

12 Es wurde der Einfluss der Infusion von bestimmtem Jonen und Arzneimitteln auf die *Konzentration anderer Jonen bestimmt*

13 Es mochte nach dieser Untersuchung scheinen, dass Kalium der erregende Stoff ist fur Kammerflimmern, dass das Kalium des Myocards bei der Ischaemie nicht beeinflusst wird durch die Plasma-Konzentration des Kaliums und zwar auf der Basis des Stoffwechsels

14 Ist nun das Kalium der das Kammerflimmern anterbende Stoff, so wurde sich aus dieser Untersuchung ergeben, dass der Kaliumstoffwechsel des Myocards bei der Ischaemie nicht beinflusst wird durch das Blut-pH, insofern das abnehmende fruhe Flimmern betroffen ist

15 Keine der Arzneimittel oder Jonen, die fur diese Untersuchung verwandt wurden, zeigten irgendeine nutzliche Wirkung hinsichtlich der Verringerung der Sterblichkeit oder des Kammerflimmerns im Anschluss an einen Coronar-Arterienverschluss

REFERENCES

1 Wiggers, C J, Wegria, R and Pineira, B "Effects of myocardial ischemia on fibrillation threshold—Mechanism of spontaneous ventricular fibrillation following coronary occlusion," *Am J Physiol*, 131 309, 1940

2 Beck, C S and Leighninger, D S "Scientific basis for the surgical treatment of coronary artery disease," *J A M A*, 159 1264, 1955

3 Hahn, R S and Kim, M "Revascularization of the heart Histologic changes after arterialization of the coronary sinus," *Circulation*, 5 801, 1952

4 Bakst, A A, Costas-Durieux, J, Goldberg, H, and Bailey, C P "Protection of the heart by arterialization of the coronary sinus," *J Thoracic Surg*, 27 433, 1954

5 Vineberg, A "Treatment of coronary artery insufficiency by implantation of the internal mammary artery into the left ventricular myocardium," *J Thoracic Surg*, 23 42, 1952

6 McAllister, F F, Leighninger, D and Beck, C S "Revascularization of the heart by vein graft from aorta to coronary sinus," *Ann Surg*, 133 153, 1951

7 Cahn, J and Melon, J M "Lecoeur sous hibernation artificielle, Anesthesie," *Par*, 11 533, 1954

8 Ribeiro, A, Sideris, H and Shumacker, H B, Jr "Ventricular fibrillation in the hypothermic state I Prevention by sinoauricular node blockade," *Ann Surg*, 143 216, 1956

9 Webb, Watts R "The effect of atrioventricular nodal blockade on fibrillation produced by electric shock," *American College of Surgeons*, Surgical Forum, San Francisco, 1956

10 Harris, A S, Bisteni, A, Russell, R A, Brigham, J C and Firestone, J E "Excitatory factors in ventricular tachycardia resulting from myocardial ischemia, potassium a major excitant," *Science*, 119 200, 1954

11 *Montgomery*, A V, Prevedel, A E and Swan, H "Prostigmine inhibition of ventricular fibrillation in the hypothermic dog," *Circulation*, 10 721, 1954

12 Hooker, D R and Kahn, N D "Evidences of an altered tissue state in ventricular fibrillation," *Am J Physiol*, 112 301, 1935

13 Brown, E B, Jr and Miller, F "Ventricular fibrillation following a rapid fall in alveolar carbon dioxide concentration," *Am J Physiol*, 169 56, 1952

14 Grumbach, L, Howard, J W and Merrill, V I "Factors related to the initiation of ventricular fibrillation in the isolated heart Effect of calcium and potassium," *Circulation Res*, 2 452, 1954

15 Bellet, S, Waserman, F and Brody, J I "Treatment of cardiac arrest and slow ventricular rates in complete A-V heart block," *Circulation*, 11 685, 1955

16 Long, J H, Oppenheimer, M J, Wester, M R and Durant, T M "Effect of intravenous procaine on the heart," *J Anesthesiol*, 10 406, 1946

17 Van Dongen, K "Action of novacaine on fibrillation of the heart," *Arch Internat Pharmacodyn*, 60 206, 1938

18 Wiggers, C J and Wegria, R "Quantitative measurement of fibrillation thresholds of the mammalian ventricles with observations on effect of procaine," *Am J Physiol*, 131 296, 1940-41

19 DiPalma, J R and Schultz, J E "Antifibrillatory drugs," *Medicine*, 29 123, 1950

20 Elek, S R and Katz, L N "Action of papaverine on the heart of the dog," *J Pharmacol & Exp Therap*, 74 335, 1942

21 Hess, M E and Haugaard, N "Effect of anti-malarial drugs on carbohydrate metabolism of cardiac muscle in vitro," *Fed Proc*, 15 92, 1956

22 Levine, S A and Fulton, M N "Effect of quinidine sulphate on ventricular tachycardia," *J A M A*, 92 1162, 1929

23 Rakow, H L "Ventricular fibrillation in acute coronary artery thrombosis during the intravenous administration of quinidine sulphate," *Ann Int Med*, 16 571, 1942

24 Moissette, E "Action de la fagarine I et de la quinidine sur la fibrillation ventriculaire primaire produite par l'occlusion coronarienne experimentale," *Compt Rend Soc de biol*, 127 233-234, 1938

25 Smith, F H, McEachern, C G and Hall, G E "Effect of intravenous administration of quinidine sulphate on development of ventricular fibrillation following sudden occlusion of circumflex branch of left coronary artery," *Am. Heart J*, 20 620, 1940

Therapy of Angina Pectoris

Evaluation of Anti-anginal Agents and Procedures

Angina pectoris has been defined as "paroxysmal chest pain of psychosomatic origin caused by myocardial ischemia "[1] It is a most changeable subjective manifestation with little consistent quantitative relation to the underlying coronary disease[2] Silber and Katz[3] emphasize that angina pectoris is pain and, hence, must be analyzed according to the physiology of sensation, quite apart from factors having to do with coronary flow As they state, "It cannot be shown that there is a high correlation between the ability of a drug to prevent electrocardiographic changes under stress and to prevent anginal pain"

Over 20 drugs and 10 surgical procedures have been advocated for the long-term treatment of angina pectoris This suggests no one remedy is effective

Assay of an anti-anginal agent or procedure is the measurement of a completely subjective sensation—the decrease in frequency and severity of chest pain Although pain perception is fairly uniform from individual to individual, persons vary greatly in their reaction from time to time Studies have shown pain to involve physical perception as well as psychological reaction Since the effectiveness of an anti anginal agent is based on a subjective report, the many factors that condition a patient's reaction must be taken into consideration Variation in these factors causes attacks of angina to differ in frequency and severity under identical circumstances in the same and in different individuals

Variation in the reaction factor and spontaneous remissions interfere with any classification of angina according to response to effort Comparison of anti-anginal agents and procedures is difficult because each has been tried on patients who often have not been classified according to degrees of severity of angina

In addition to its pharmaceutic action, every drug has a placebo effect that is derived from the urgent desire of patients for relief and from the physician's enthusiam Thus the total drug effect is equal to its active effect plus its placebo effect Placebos have been shown by Evans and Hoyle[4] to relieve the pain of angina pectoris satisfactorily in 38 per cent of their patients Beecher[5] reviewed 15 studies involving over 1,000 patients in which placebos were found to have a degree of effectiveness measuring 35 2 plus or minus 2 2 per cent

There is an inherent therapeutic effect of an agent or therapy proportionate to its impact on the psyche Thus, an injection has a greater effect than a pill, and a surgical procedure, the greatest effect of all The counterpart of a placebo in the evaluation of a surgical technic is the sham operation

Besides the placebo effect of the pill or procedure, it has been shown that the physician-patient relationship decreases the frequency of chest pain in patients with angina without placebos [6] It is essentially in the rapport period—the initial stages of therapy—that a good psychologic relationship is established between physician and patient

As the double-blind technic by passes the placebo effect, so multiple control periods in the post-rapport period circumvent the effects of the doctor-patient relationship [7]

The number of suitable patients with stable angina usually is too small to be statistically significant, and the daily attack of chest pain too infrequent to allow per cent improvement (as an expression of decrease in frequency of attacks) to be an accurate measurement in the assay of anti-anginal agents or procedures [8] The results of a study[9] in which an anti-anginal agent is stated to have produced 50 per cent improvement in 48 per cent of 23 cases should be compared with another study[8] of 24 cases, in which 63 per cent of the patients were improved 75 per cent, by the ceremony of drug research and good doctor-patient relationship, which were the only therapeutic factors operating

Medical Treatment

The Long-Acting Nitrates

The currently most popular representative of this group is pentaerythritol tetranitrate (Peritrate), in 10 to 20 mg oral tablets, three to four times a day Peritrate was found by Winsor and Humphreys to be helpful in preventing anginal attacks, but neither multiple successive control periods nor the double-blind technic was employed Russek et al believe that Peritrate protects selected patients with coronary artery disease from electrocardiographic changes produced by an exercise test They did not demonstrate, however, that Peritrate decreased the frequency of attacks of angina pectoris, a completely subjective manifestation Salans, Silber and Katz, Friedberg and Talley, et al found Peritrate ineffective in the treatment of cardiac pain They found only one of 25 persons with angina pectoris to respond to Peritrate in the post-rapport period

Another popular long-acting nitrate, triethanolamine trinitrate (Metamine) in daily doses of 6 to 16 mg was reported by Palmer and Ramsey, and Fuller and Kassell as being effective in the prevention of anginal pain In neither of these studies were multiple successive periods without medication provided as controls, nor was the double-blind technic employed Silber and Katz, and Friedberg failed to find Metamine effective in the treatment of anginal pain Friend et al,[10] and Cole et al [6] found Metamine to be ineffective when tested with the double-blind technic and multiple successive control periods

The Xanthines

Gold et al [11] traced the use of xanthine derivatives back to 1895 and commented that beneficial results in percentages of up to 80 per cent were from reports of clinical experiences rather than controlled investigations Their experience agrees with that of Evans and Hoyle[4] who found that when xanthines were tested against placebo controls, the xanthines did not show

themselves to be worthy even of trial in the routine treatment of cardiac pain

Oscharoff[9] claims that Elixophyllin in one to two ounce doses at four hour intervals is useful in the treatment of angina pectoris He did not rule out, by utilization of the double-blind technic, the placebo effect or the cerebral effect of the alcohol of the elixir Friedberg[12] has remarked that xanthine drugs have been marketed in combination with sedatives, usually phenobarbital, which may assure the benefit of at least one drug in the combination

Khellin and Papaverine

The importance of the double-blind technic in by-passing the bias of the physician and the suggestibility of the patient in the evaluation of an anti-*anginal agent is illustrated by Gold*[13] in discussion of khellin "When a physician knew which was drug and which was placebo, a large number of patients appeared to obtain relief of cardiac pain from khellin When the study was repeated in the same group of patients, but neither physicians nor patients were aware of the identity of the agents, then the placebo and khellin could not be distinguished with respect to the effect on cardiac pain" Another group of investigators similarly had to reappraise their experience with khellin and with papaverine in angina when they retested these drugs employing the double-blind technic[7]

Anti-thyroid Therapies

To reduce the patient's metabolism, diminish the work of the heart and its need for coronary flow, attempts have been made to ablate the thyroid gland by thiourea derivatives, radio-iodine and surgery

The thiourea derivatives—mainly thiouracil, and propylthiouracil reduce the activity of the thyroid gland and are effective only so long as administered They require prolonged therapy and have toxic effects, particularly on the hemopoietic system

Radioactive Iodine

Where it is available, hypothyroidism is more easily induced by radio-iodine than by the thiourea derivatives or thyroidectomy Blumgart et al,[14] report 75 per cent of 720 patients to have worthwhile improvement It should be noted that the good results are achieved at the expense of introducing myxedema, which has its own set of uncomfortable symptoms For this, small daily doses (6 to 30 mg) of thyroid can be administered to restore a metabolic rate consistent with comfort—usually minus 10 to minus 25 per cent

Antithyroid therapies should be reserved for that small group of patients with angina pectoris whose symptoms are so severe that the introduction of myxedema is warranted Since the symptoms of hypothyroidism would differentiate treated persons from the controls, double-blind technics are not applicable

Surgical Treatment

Surgical procedures are indicated when severe angina has persisted for at least six months, or has become intractable despite every effort to elim-

inate or alleviate any possible contributory factor and all other means of treatment have been exhausted

Operations on Nerves

All painful impulses pass through the upper four or five thoracic ganglia, their rami communicantes and the corresponding thoracic posterior spinal nerve roots More successful results have been obtained by excision of the upper four or five thoracic ganglia than with paravertebral alcohol injections

Production of a Collateral Blood Supply to the Heart

Currently the most popular surgical procedures are the Thompson, Beck I, Vineberg operations and the ligation of branches of the internal mammary artery The Beck I operation consists of abrasion of the epicardium and lining of the parietal pericardium, application of an irritant, 0 2 gm of powdered asbestos, to these surfaces, partial occlusion of the coronary sinus where it enters the right atrium and graft of the parietal pericardium and mediastinal fat to the surface of the heart The Thompson procedure is the production of adhesions by the introduction of powdered silica (talc) into the pericardial cavity While it is claimed that attacks of angina are prevented or diminished in frequency in 80 per cent of patients by the Thompson procedure, there is a 12 per cent operative mortality Vineberg implants the internal mammary artery with an open freely bleeding intercostal branch directly into the left ventricular myocardium, 70 per cent improvement in 29 patients is reported

That the impressiveness of the surgical procedure may be the major part of its therapeutic effect is suggested by Lillehei[15] who has applied the double-blind technic to the ligation of the internal mammary artery His preliminary results indicate just as good results with the sham operation (skin incision) as with the operation itself Ripstein[16] initially has found just as good results from the sham operation as from coronary vein ligation with or without poudrage

Vineberg[17] has found that it is necessary to wait at least six months after surgery, beyond which the psychologic impact does not persist, before attempting to decide how much benefit the patient has obtained He suggests careful before and after evaluations of the patients by three members of a team of medical men, one of whom is a psychiatrist

Psychosocial Therapy

The vise-like pain of severe angina, a recurrent symbol of sudden death or incapacitating disease, must be actively combated by a positive approach The patient should be assured that he is going to live, and of the probability of a long and productive life if he cooperates in the treatment To be told that he is not going to die, is too negative, the word death should not enter into a discussion of his condition The patient may be greatly encouraged by being informed that cardiac patients often outlive other people because they lead a more moderate life He should be seen frequently so that his confidence is restored, and to give opportunity for the emotional tensions arising from his domestic life and occupation to be ascertained and properly handled The patient's functional capacity should be measured against

the demands of his job by the physician or a work classification unit where available Then he should be encouraged to live as near a normal life as he is able Eskwith[18] used a good physician-patient relationship, tranquilizing drugs—e g meprobamate and phenobarbital—to help patients handle the emotional tensions arising from family and business life With an over-all medical approach, he was able to improve 90 per cent, and restore 80 per cent of patients with angina pectoris to active employability

It is quite probable that psychosocial therapy accounts for many of the good effects attributed to drugs, radiation to the thyroid, and surgery

ADDENDUM

Since this paper was submitted for publication, Cossio and Master have reported that Ipronıazid (Marsilid) has decreased the frequency of attacks of angina pectoris If confirmed by the double-blind technic and trial through multiple control periods in the post-rapport stage, this avenue of therapy may be rewarding (Cossio, Pedro "The Treatment of Angina Pectoris and Other Muscular Pain Due to Ischemia with Iproniazid and Isoniazid" *Am Heart J*, 56 113, 1958), (Master, A Personal Communication)

SEYMOUR L COLE, M D, F C C P
Beverly Hills, California

REFERENCES

1 *Blakiston's New Gould Medical Dictionary*, 2nd Edition, McGraw-Hill Book Co, 1952, p 76
2 Katz, L N "Mechanism of Pain Production in Angina Pectoris," *Am Heart Journal*, 10 322, 1935
3 Silber, E H and Katz, L N "Coronary Dilators and Angina, Reappraisal," *J A M A*, 153 1075 1953
4 Evans, W and Hoyle, C "The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris," *Quart J Med*, 2 311, 1933
5 Beecher, H K "The Powerful Placebo," *J A M A*, 159 1602, 1955
6 Cole, S L, Kaye, H and Griffith, G C "Assay of Anti-anginal Agents, I A Curve Analysis with Multiple Control Periods," *Circulation*, 15 405, 1957
7 Cole, S L, Kaye, H and Griffith, G C "Assay of Anti-anginal Agents, II The Rapport Period," To be published in J A M A
8 Cole, S L, Kaye, H and Griffith, G C "Assay of Anti-anginal Agents, III Per Cent Improvement," To be published
9 Oscharoff, A "Therapeutic Effectiveness of Elixophyllin as Compared with Aminophylline in Severe Angina Pectoris," *New York State J Med*, 57 2975, 1957
10 Friend, D G, O'Hara, J P and Leving, H D "Action of Triethanoloamine Trinitrate (Metamine) in Angina Pectoris," *Am Heart J*, 48 775, 1954
11 Gold, H G, Kwit, N T and Otto, H "The Xanthines, Theobromine and Aminophylline in the Treatment of Cardiac Pain," *J A M A*, *108 2173, 1937*
12 Friedberg, C K *Diseases of the Heart*, 2nd Edition, W B Saunders Company, Philadelphia, 1956, p 481
13 Gold, H "Conference on Therapy How to Evaluate a Drug," *Am J Med*, 17 722, 1954
14 Blumgart, H L, Freedberg, A S and Kurland, G S "Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine Summary of Results in Treatment of 1,070 Patients with Angina Pectoris or Congestive Failure," *J A M A*, 157 1, 1955
15 Lillehei, C W Personal Communication
16 Ripstein, C Personal Communication
17 Vineberg, A and Walker, J "Six Months to Six Years Experience with Coronary Artery Insufficiency Treated by Internal Mammary Artery Implantation," *Am Heart J*, 54 851, 1957
18 Eskwith, I S "The Holistic Approach to Angina Pectoris," *Am Heart J*, 55 621, 1958

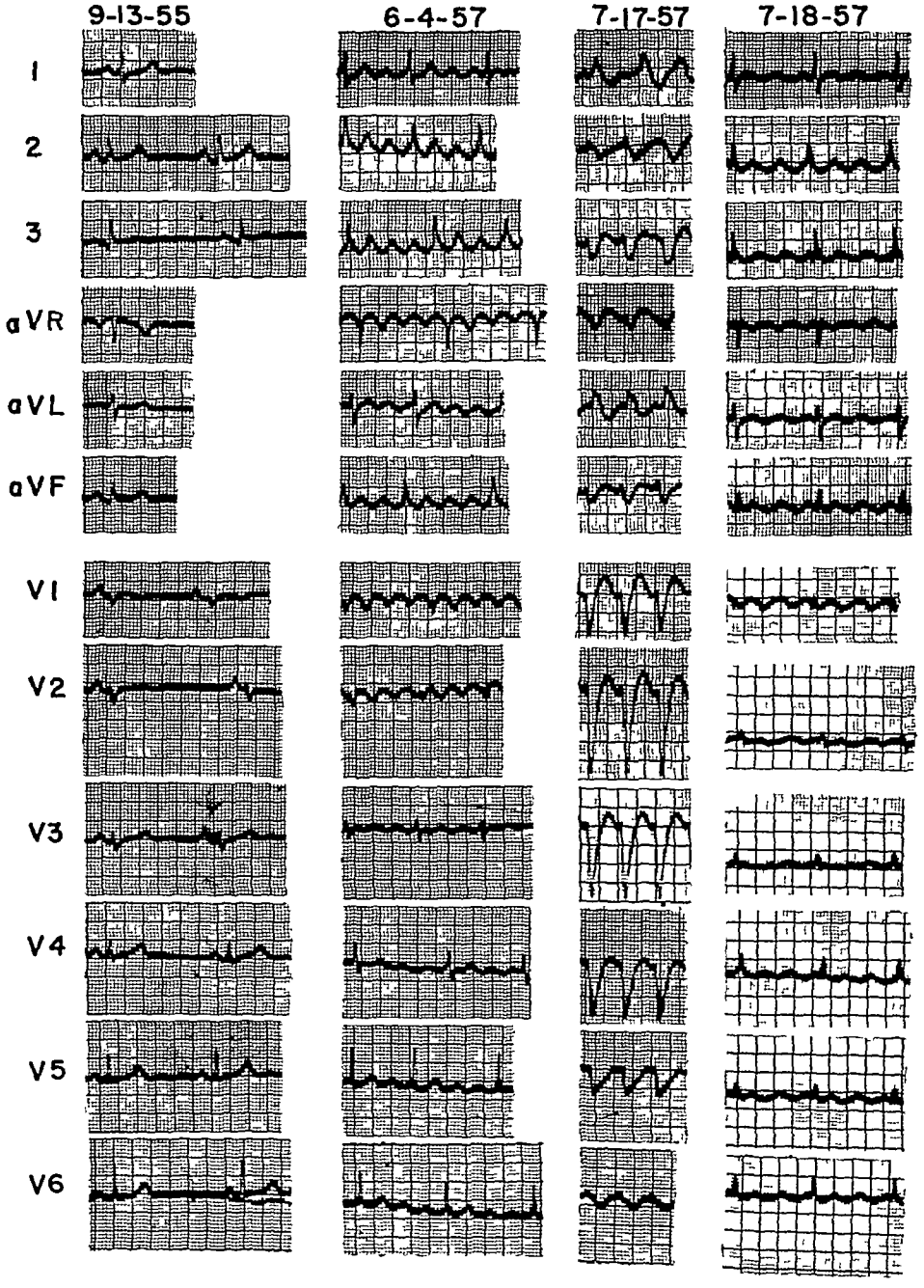
ELECTROCARDIOGRAM OF THE MONTH

The author would be pleased to receive comment and controversy from readers in relation to explanations offered

---

Chronic Auricular Flutter

Mrs A H is a 48 year old white woman who has mitral stenosis and aortic insufficiency with mild left ventricular hypertrophy noted in the chest x-ray She has known about the cardiac murmurs since 1948 Her blood pressure is



130/60 She had normal sinus rhythm until 1955 (see illustration) and never required digitalis On June 6, 1956 she was found to have 3 1 auricular flutter with a ventricular rate of 121 beats per minute and manifestations of decreased cardiac reserve After appropriate digitalization, her cardiac reserve improved and the degree of a-v block increased to 5 1 with a ventricular rate of 64 The patient was given 0 2-0 4 Gms of quinidine orally four *times daily at home* About four days later normal sinus rhythm reappeared

On June 4, 1957 (see illustration) she again had auricular flutter with a varying (3 1 and 4 1) degree of a-v block and congestive heart failure After the latter had improved following regulation of digitalis intake, quinidine 0 5 Gms four times daily was again administered while she was ambulatory for about one week Auricular flutter did not disappear and she had symptoms of cardiac consciousness which were aggravated by anxiety regarding her domestic problems

She was hospitalized and received anticoagulant medication as well as maintenance digitalis Several days later, an attempt at reconversion to normal sinus rhythm was made by administering quinidine 0 4 Gms every two hours for three doses One hour after the last dose, she suddenly developed ventricular tachycardia with abnormally wide QRS complexes (see illustration July 17, 1957) together with mild peripheral circulatory failure and hypotension These adverse manifestations disappeared spontaneously in about half an hour and auricular flutter (with 4 1 a-v block) reappeared as shown in the illustration (July 18, 1957)

Two months after this episode of quinidine toxicity, she still had auricular flutter with ventricular rate averaging 80 beats per minute She is taking maintenance doses of digitalis only The auricular flutter has remained despite a trial of other, and less toxic, dosage schedules of quinidine

She has had chronic auricular flutter for almost one and a half years Earlier rather than later, in the course of auricular flutter, quinidine will often convert this arrhythmia to normal sinus rhythm although this is not a fixed rule Such patients whom the author has followed do well when they are treated as though they had chronic auricular fibrillation, that is, when the ventricular rate is controlled with digitalis

STEPHEN R ELEK, M D, F C C P
Los Angeles, California

(Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Co-Chief, Cardiac Clinic, Cedars of Lebanon Hospital, and Consulting Cardiologist, Veterans Administration)

Case Report Section

Subacute Cor Pulmonale Due to Metastatic Carcinomatosis of the Lung Report of a Case with Autopsy Findings

JOSEPH T GIAMMALVO, M D * and STEWART H JONES, M D **
Boston, Massachusetts

Introduction

Cor pulmonale is divided into the acute and chronic forms according to the duration of the disease In the former the clinical picture of strain on the right side of the heart is manifested over a period of hours or several days and ends either fatally or in complete recovery of the patient The commonest cause of this condition is pulmonary embolism Chronic cor pulmonale is clinically manifested over a period of many months and is due to a multiplicity of causes such as valvular disease of the heart or chronic pulmonary disease In 1937 Brill and Robertson[1] described a third form as subacute cor pulmonale in which the disease runs a fairly rapid clinical course extending over a period of several weeks during which severe dyspnea is the outstanding clinical symptom In this paper we wish to report a case of subacute cor pulmonale and review briefly the literature on this subject in order to re-emphasize its clinical and pathologic features

Report of a Case

A 58 year old housewife, mother of two, first came to the Lahey Clinic July 5, 1953 She had discovered a nodule in her left breast four years previously, and had done nothing about it Recently it had become larger and caused mild discomfort A non-tender, fixed, hard, irregular mass was present in the left outer quadrant Axillary lymph nodes were not enlarged

Two days later a radical left mastectomy was done and the pathologic diagnosis was scirrhous carcinoma with metastases to 22 of 29 lymph nodes Following operation she received 21 x-ray treatments from August 2 to September 2, 1953

Periodic check-up examinations from 1953 on failed to reveal any recurrence until a visit on September 26, 1955, when she complained of cough, pallor and chest pain Pressure elicited marked tenderness in the left axilla Hemoglobin was 9 gm per 100 cc, hematocrit 27, red blood cell count 3,010,000, white blood cell count 3,750, and the differential count was normal The chest roentgenogram showed slight fibrosis in the left upper lobe, slight cardiac enlargement and increased density in the ribs A film of the left ribs showed fracture of the eighth in the posterior axillary line A roentgenogram of the spine, two weeks later, revealed spotty demineralization suggestive of metastatic disease She received five x-ray treatments over the spine with moderate relief of upper back pain Orteton methyl tablets, 10 mg every other day, for 20 doses was also prescribed

The first definite evidence of osseous metastases was in a skull roentgenogram on December 2, 1955, which showed a mottled destructive change throughout the entire calvarium with a large radiolucent area in the left supraorbital region A chest roentgenogram gave the same appearance of mild fibrosis as previously Her complaints were exertional dyspnea and moderate discomfort in chest and spine

There was gradual increase in the dyspnea and on January 19, 1956, it was so severe she was brought to the hospital by ambulance On examination she was cyanotic and severely dyspneic, struggling to breathe Oxygen by nasal catheter gave no perceptible

*Department of Pathology, Tufts University School of Medicine
**Department of Internal Medicine, The Lahey Clinic

relief She was too ill to have pulmonary function tests, but it seemed by auscultation that lung volumes were normal and it was not obvious why there was such respiratory difficulty A chest roentgenogram again showed mild fibrosis as before, but in both lungs now The heart was slightly enlarged and the vascular shadows prominent

Treatment was symptomatic with oxygen and small doses of narcotics There was increasing cyanosis, and the uncontrollable dyspnea continued until she died 46 hours after admission The clinical diagnosis was carcinomatosis involving the skull, ribs, and vertebrae secondary to carcinoma of the breast, cor pulmonale secondary to pulmonary fibrosis secondary to x-ray therapy, and terminal pneumonia

FIG 1

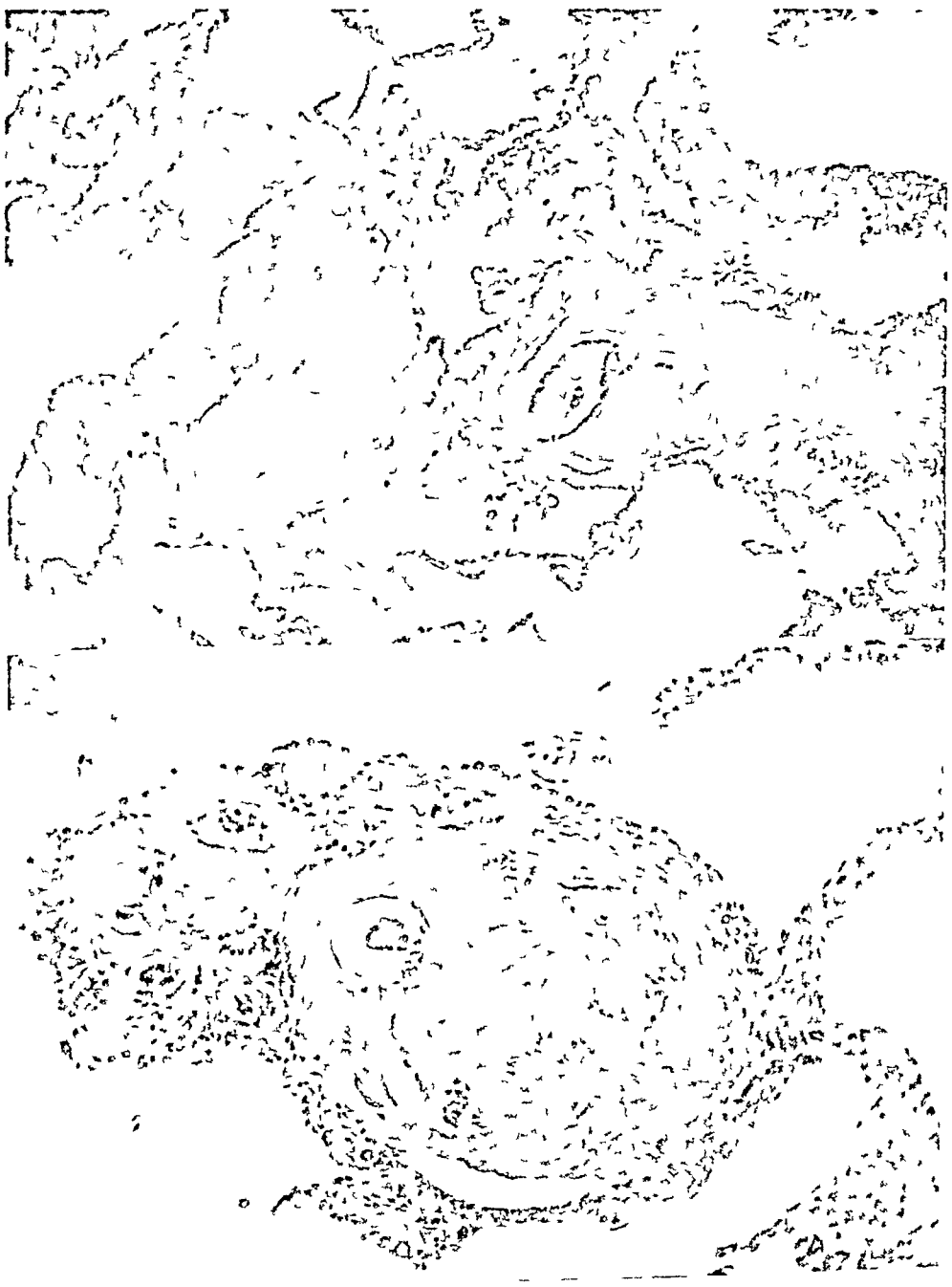


FIG 2

Figure 1 This section of lung shows two small pulmonary arteries with a narrowed lumen due to a greatly thickened intima and occlusion of a third artery by tumor emboli and an organized thrombus.—*Figure 2* Cross section of a small pulmonary artery showing an organized obliterating thrombus with tumor emboli Note the presence of tumor cells in the perivascular lymphatics

*Autopsy Findings**

External examination revealed the body to be that of a moderately obese elderly woman with a left radical mastectomy scar and signs of chronic lymphedema in the left arm There was no evidence of recurrent tumor at the operative site However, two small tumor nodules were palpable over the occiput The neck veins were distended, and the ankles showed a mild pitting edema Examination of the peritoneal cavity disclosed a distended stomach but no signs of metastases When the sternum was removed, voluminous lungs were seen filling the pleural cavities and approximating each other in the midline Each pleural cavity was free of fluid The lungs were bound posteriorly and laterally by several thin fibrous adhesions The right lung weighed 350 gm, the left 430 gm Each lung was distended, crepitant and fluffy throughout except for minimal marginal atelectasis Each showed glistening gray pleural surfaces with minimal anthracotic pigmentation A fine granularity was noted over the right lower lobe and the anterior surface of the right upper lobe Each lung presented a grayish, dry and almost bloodless cut surface with the exception of several subcrepitant, firm, dark red to green areas of discoloration in the right upper and left lower lobes The bronchi contained a small amount of greenish mucoid material There were no distinct tumor masses in the lung, and the peribronchial and paratracheal lymph nodes were grossly free of metastases The larger branches of the pulmonary artery showed deposits of lipid in the intima

When viewed *in situ* the heart appeared to be somewhat enlarged due to a prominent right ventricle and pulmonary conus The venae cavae and the innominate veins were distended with blood A transverse section through the ventricles resulted in the outpouring of an excess of fluid blood from the right side of the heart, yet exploration of the pulmonary artery and its major branches revealed no emboli

The heart weighed 380 gm The right auricle was slightly dilated and hypertrophied There was also slight dilatation of the tricuspid valve which measured 10 5 cm The right ventricular wall measured 0 4 gm in thickness along the inflow tract Its papillary muscles were large and the trabeculae carneae were broad and thick The wall of the pulmonary conus was also hypertrophied and the trabeculae carneae were flat The pulmonary valve leaflets were unaltered, and the dilated valve measured 8 2 cm Changes in the left side of the heart included minimal dilatation and hypertrophy of the left ventricle which measured 1 4 cm in thickness The coronary arteries showed mild nonocclusive atherosclerosis

Examination of the organs of the abdomen disclosed no evidence of metastatic tumor Metastases were present, however, in the lumbar vertebrae and the left eighth rib

Microscopic Examination

The significant histologic findings were present in the lung and bones In the sections of lung taken from all five lobes, some of the small pulmo-

*A-56-1, *Booth Memorial Hospital*

nary arteries, arterioles and most of the lymphatic vessels were obstructed by masses of well preserved and apparently viable tumor cells These cells were also present in alveolar capillaries In addition, old organized thrombi with or without tumor emboli partially or completely occluded the lumen of some of the small pulmonary arteries, while others showed a narrowed lumen as a result of concentric intimal fibrosis (Figs 1 and 2)

Although a considerable number of the small arterial branches showed these obstructive lesions, there were vessels that appeared to be spared A moderate degree of emphysema and focal atelectasis was present, and there was evidence of terminal aspiration of gastric content with no inflammatory response

The vertebral bones were the site of metastatic tumor with fibrosis of the marrow and hyperplasia of the cancellous bone Tumor cells were demonstrable in many of the blood sinusoids

The anatomic diagnosis was status following left radical mastectomy for carcinoma of the breast, pulmonary carcinomatosis with cor pulmonale, metastatic carcinoma involving lumbar vertebrae, left eighth rib and skull, chronic lymphedema of the left arm, agonal aspiration of gastric content

Comment

The Clinical Picture of Subacute Cor Pulmonale

The outstanding clinical features presented by this case were severe dyspnea and cyanosis not relieved by the administration of oxygen, the presence of linear shadows in both lung fields and slight enlargement of the heart in roentgenograms, and a clinical course of several months' duration These signs and symptoms occurred in a patient with evidence of a metastatic tumor in the skeletal system and with a negative history of previous cardiopulmonary disease The picture here was one of a rapidly progressive cor pulmonale in which the underlying cause was not evident ante mortem

In 1937 Brill and Robertson reported a case and reviewed two others that presented this general clinical pattern with the exception that the primary tumors were gastric in origin and not diagnosed clinically They designated this clinical picture of rapidly progressive failure of the right side of the heart as subacute cor pulmonale to distinguish it from the acute and chronic forms Subsequent case reports[3, 4] have appeared in the literature under this title, each showing this general clinical pattern

The Pathologic Substrate of Subacute Cor Pulmonale in Pulmonary Carcinomatosis

The gross autopsy findings in the present case report were meager indeed There was evidence of pulmonary hypertension in the form of dilatation and hypertrophy of the right side of the heart with no obvious gross lesion to account for it Careful inspection of the lung revealed the linear white streaks of dilated lymphatics and a fine granularity within the substance of the lung The cause of the pulmonary hypertension became evident in the histologic sections in the form of obstructive lesions involving

the pulmonary arteries These lesions were of three types (1) organizing arterial thrombi with or without the presence of tumor emboli, (2) tumor emboli lodged in the lumen of small arteries and arterioles, and (3) pulmonary arteriosclerosis of the obliterative endarteritic type

These obstructive vascular lesions appeared to be related The frequent occurrence of tumor cells in organizing thrombi suggested that the latter may have been initiated by the presence of the former Furthermore, the location of obliterative endarteritis proximal to points of obstruction in the longitudinal views of arteries suggested a causal relationship between the two lesions This view is in opposition to that expressed by von Meyenburg,[6] Greenspan,[2] Brill and Robertson[1] who considered the obliterative endarteritis as an effect of perivascular lymphatic carcinomatosis Wu's[7] objection to this explanation was based on the observations that only a few cases of lymphatic carcinomatosis showed these arterial changes and that even in these, many vessels were exempt That the cor pulmonale was related to the obstructive arterial lesions and not directly to lymphatic carcinomatosis was borne out by the studies of Morgan [5] He found that out of 78 cases of diffuse carcinomatosis of the lung only 11 showed right ventricular hypertrophy and of these, 10 showed obstructive arterial lesions in the form of vascular fibrosis or recent thrombosis

It would appear then that the clinical picture of subacute cor pulmonale resulted when a sufficient number of pulmonary arteries were progressively obstructed by tumor emboli and thrombosis with the resultant obliterative endarteritis producing progressive increments of pulmonary hypertension that proved fatal within a matter of weeks

Sites of the Primary Tumor in Reported Cases of Pulmonary Carcinomatosis

The primary site of the tumor in the majority of the reported cases was the stomach Other primary sites included bronchus, breast, prostate, pancreas, large bowel, biliary tract and rectum Since the primary tumor frequently remained undiagnosed during the life of the patient and since the symptomatology of subacute cor pulmonale is sufficiently distinctive, the presence of the latter should alert the clinician to the possibility of an occult malignant tumor that had metastasized to the lung in the form of diffuse vascular carcinomatosis

REFERENCES

1 Brill, I C and Robertson, T D "Subacute Cor Pulmonale," *Arch Int Med*, 60 1043, 1937

2 Greenspan, E B "Carcinomatous Endarteritis of Pulmonary Vessels Resulting in Failure of Right Ventricle," *Arch Int Med*, 54 625, 1934

3 Krygier, J J and Brill, I C "Subacute Cor Pulmonale Due to Metastatic Carcinomatous Lymphangitis of Lungs," *Northwest Med*, 41 319, 1942

4 Mason, D G "Subacute Cor Pulmonale," *Arch Int Med*, 66 1221, 1940

5 Morgan, A D "The Pathology of Subacute Cor Pulmonale in Diffuse Carcinomatosis of the Lungs," *J Path & Bact*, 61 75, 1949

6 Von Meyenburg, H "Zur Kenntnis der lymphangitis carcinomatosa in lungen und pleura, Cor —Bl f schweiz," *Aerzte* 49 1668, 1919

7 Wu, T T "Generalized Lymphatic Carcinosis (Lymphangitis Carcinomatosa) of Lungs," *J Path & Bact*, 43 61-76, 1936

Metastatic Pulmonary Melanoma of 15 Months' Duration

MILTON B ROSENBLATT, M D , F C C P * and JAMES R LISA, M D **
New York, New York

The lung is a common site for metastatic foci from extrapulmonary malignancies Abrams[1] found the lung involved, metastatically, in 46 5 per cent of 1,000 autopsied cases of carcinoma On the basis of radiographic evaluation, Pendergrass[2] estimated the incidence of pulmonary metastases from all carcinomas to be 30 per cent and as high as 75 per cent from renal cancer In general, the secondary deposits in the lung appear on the roentgen film as bilateral, multiple, rounded shadows of varying size and are the result of hematogenous embolic spread The primary tumors usually associated with this type of lesion arise from the thyroid, genitourinary tract, intestinal tract and bones

Malignant melanoma commonly involves the lung by way of vascular spread but the relative rarity of the tumor usually precludes its inclusion in the differential diagnosis of pulmonary lesions In a radiographic study of 314 cases of pulmonary metastases, Minor[3] found 15 secondary to melanoma The average time that elapsed between the onset of the primary lesion and the appearance of pulmonary metastases was 32 5 months and the interval between appearance of the metastases and death was 4 1 months Most of the patients with melanomatous pulmonary deposits are diagnosed in the preterminal stages of the disease The following case of malignant melanoma is therefore of unusual interest in that there was roentgen evidence of extensive metastases 15 months prior to death, during the greater part of which time the patient was completely asymptomatic The diagnosis of melanoma was established 14 months after the initial roentgen observation of the pulmonary nodules

The patient was a 61 year old, white clerk who presented himself at the Union Health Center on August 22, 1952 for a routine check-up There was no significant complaint With the exception of post-nasal discharge of 20 years' duration he had enjoyed excellent health The past history revealed an appendectomy at age 15 His parents had died of heart disease in the eighth decade Three brothers were alive and well His appetite was good, bowels were regular, once daily, there was no genitourinary or cardiovascular symptom The physical examination and routine laboratory studies of the blood and urine were negative A routine chest x-ray film (Figure 1) disclosed several large round nodules involving both lung fields A tentative diagnosis of metastatic carcinoma was made and he was referred to the Memorial Hospital for further study

A comprehensive examination was made at the Memorial Hospital and repeated at the Mount Sinai Hospital Roentgen examination of the genito-urinary tract, entire intestinal tract, gall bladder and bones failed to reveal a primary lesion Bronchoscopy and esophagoscopy were negative Cytologic examination of the sputum, bronchial washings, gastric washings and urine were negative He was advised to undergo exploratory surgery of the thorax and the abdomen on different occasions but refused Between hospital and clinic visits he continued working and had no complaint other than the anxiety induced by the medical interest in his condition

*Visiting Physician, Metropolitan and Bird S Coler Hospitals
**Director of Pathology Service, New York City Department of Hospitals

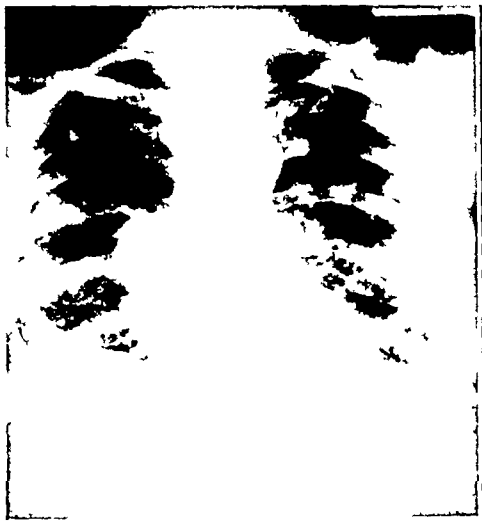


FIGURE 1

FIGURE 2

Figure 1 Routine chest film, August 22, 1955, showed large nodular densities in both lung fields No pulmonary symptoms (*Courtesy of The Union Health Center*)— *Figure 2* Films on October 5, 1956 (14 months later) showed a slight increase in the rounded densities previously observed No pulmonary complaints during the interval between films

Examination by one of us (M B R) on May 1, 1956 found him to be well developed and nourished with evidence of recent weight gain There were multiple pigmented nevi distributed over the thorax The pupils reacted to light and accommodation and the external ocular movements were normal The nasopharynx appeared negative There were no palpable cervical or axillary nodes The thorax was symmetrical, breath sounds vesicular and percussion note unimpaired The cardiac outline was within normal limits, the sounds were of good quality, regular sinus rhythm, no murmur, ventricular rate of 80 per minute The blood pressure was 140/80 There was a post-operative scar on the abdomen The liver and spleen were not palpable Rectal examination was negative There was no peripheral edema The reflexes were active and equal, bilaterally

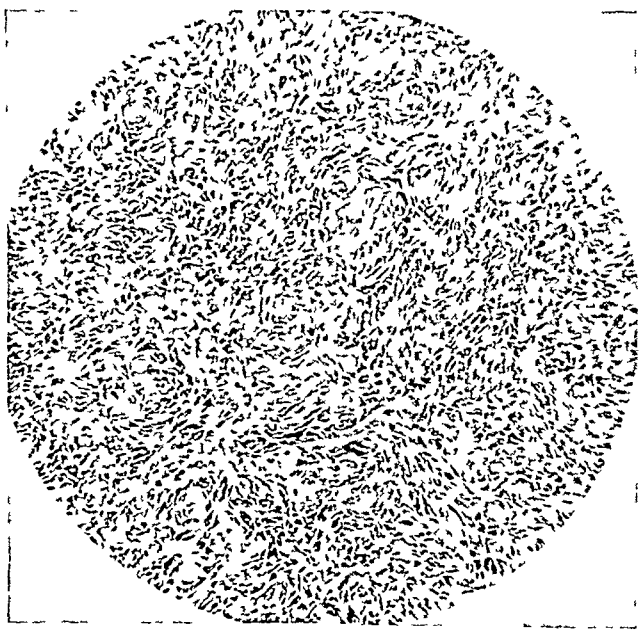


FIGURE 3 Metastatic melanoma of lung showing the marked anaplasia

Roentgen examination of the chest showed no definite change in the number or size of the shadows seen on the film of August 22, 1955 The electrocardiogram showed left axis deviation The sedimentation rate was 35 mm per hour (Westergren) The blood count revealed hemoglobin of 82 per cent, 4,400,000 red blood cells, 9,750 white blood cells with normal differential The urinalysis was negative Intradermal tests were negative for coccidiomycosis and positive for histoplasmosis Papanicolaou smears of the sputum were negative The gastric washings were negative for tubercle bacilli

He had no complaint until October 1956 when he suddenly became aware of spasmodic twitching of the right shoulder muscles and of the tongue This was followed by weakness in the lower extremities, right hemiplegia and dysarthria The pulmonary status was unchanged clinically and the roentgen examination (Figure 2) showed slight increase in the diameter of the nodular densities previously observed He was admitted to the neurologic service of the Mount Sinai Hospital where a small pigmented area was noted on the lower lip near the buccal mucosa Biopsy revealed the lesion to be a malignant melanoma He was transferred to the Doctors Hospital on November 19, and died on November 26, 1956 after a series of convulsive seizures

Necropsy examination revealed metastatic melanoma of the lungs, adrenals, jejunum, ileum, colon, ribs and brain Gross inspection of the lungs showed tumor masses scattered throughout all the lobes The masses were colored dark brown, were firm in consistency and measured up to 4 5 cm in diameter The right upper lobe contained one mass, the middle lobe had two, and the lower lobe four masses The left upper lobe and lower lobe had four and five masses, respectively The intervening parenchyma appeared normal There was mild hyperemia of the trachea and main bronchi

Microscopic examination showed the pulmonary masses (Figure 3) to consist of extremely bizarre cells having a spindle appearance and displaying anisocytosis, macronucleation, hyperchromatism and mitoses There were focal areas of nests heavily pigmented by melanin The non-tumerous portions of the lungs were normal

The tumor masses in the adrenals were similar to those in the lungs and occupied the entire thickness of the cortex In the intestinal tract, the tumors involved the muscle and submucosa and were about 2 cm in size in the jejunum and ileum and smaller in the colon *The marrow of the third and fourth left ribs was diffusely brown to black* and presented a striking appearance The vertebrae were normal The brain was deeply pigmented with the same cellular changes In the cerebellum, the lesions were limited to the cortical gray and were characterized by necrobiosis and hemorrhage

In all probability, the primary site of the melanoma was the lesion in the mouth, although this was not suspected for 14 months after the pulmonary metastases had been recognized The large number of pigmented nevi scattered over the thorax probably contributed to the diagnostic confusion It is also possible that in the course of the convulsive seizures, he had bitten his lip and drawn attention to the small pigmented area According to Pack[4, 5] and Moore,[6] the sinonasal region is an infrequent primary site for malignant melanoma, comprising approximately 2 per cent of the total Origin from the lips is extremely uncommon

REFERENCES

1 Abrams, H L, Spiro, R and Goldstein, N "Metastases in Carcinoma, Analysis of 1000 Autopsy Cases," *Cancer*, 3 74, 1950

2 Pendergrass, R and Americus, G "Lung Metastases," *J M A Georgia*, 43 338, 1954

3 Minor, G R "A Clinical and Radiologic Study of Metastatic Pulmonary Neoplasms," *J Thoracic Surg*, 20 34, 1950

4 Pack, G T, Gerber, D M and Scharnagel, J M "End Results in the Treatment of Malignant Melanoma," *Ann Surg*, 136 905, 1952

5 Pack, G T, Lenson, N and Gerber, D M "Regional Distribution of Moles and Melanoma," *A M A Arch Surg*, 65 862, 1952

6 Moore, E S and Martin, H "Melanoma of the Upper Respiratory Tract and Oral Cavity," *Cancer*, 8 1167, 1955

Editorial

A World of Peace

The traditional forms of education, political oratory, literature and religious ceremonies have conditioned the attitudes and spontaneous reactions of individuals and nations, and have created unnecessary barriers among them Through science and natural philosophy we learn the truth or, to be more exact, with these aids at our disposal, we attain the most trustworthy conception possible of ourselves and the total nature of things Scientific and philosophical knowledge aid man to gain wisdom and understanding

Today, Kipling's oft-quoted couplet, "East is East and West is West, and never the twain shall meet" is irrevocably outdated The situation presented by Kipling arose because the East, in its contemplation on aesthetic components of life, and the West in its pursuit of known components, tended to brand as illusory and evil any knowledge other than their own There is no reason why the civilizations of the East and West cannot meet

The international ideological issue today is not a simple question of good and bad, but a complex conflict between different conceptions of what is good These different conceptions can be reconciled through personal contacts on international platforms This will undoubtedly lead to intelligent appreciation and understanding of the ideological differences which are more imagined than real

We want to live in a new sort of world, a world of peace The flowering of science, which has rendered war absurd, also gives us wealth, comfort and freedom from disease in the body and mind Our contest for position in the intricate fabric of society no longer need require that those who fail shall undergo suffering

Medical science which is devoted to the alleviation of human suffering, is neither individual nor national, but international Institutions and learned bodies devoted to scientific research are not concerned with Man's origin, his religion, race or country Their doors are open to all The international congresses on diseases of the chest, sponsored by the American College of Chest Physicians, afford excellent opportunities for the medical men and women throughout the world to meet, not only to exchange ideas on scientific matters, but also to create international good-will and understanding Seeing other people and seeing ourselves as others see us, makes us wise Wisdom leads to understanding Understanding begets tolerance, tolerance, in its turn, leads to "Peace on earth and good will to all men"

RAMAN VISWANATHAN, M D , F C C P *

New Delhi, India

*Regent for India

PROCEEDINGS OF THE 24TH ANNUAL MEETING

Board of Regents and Board of Governors

The Board of Regents and the Board of Governors of the College held their annual meetings on Wednesday and Thursday, June 18 and 19, at the Fairmont Hotel, San Francisco, at the time of the 24th Annual Meeting of the College. The following Regents, Governors, Chapter Delegates and guests were officially registered

John F Briggs St Paul Minnesota, Chairman Board of Regents
David H Waterman Knoxville Tennessee Chairman Board of Governors

Osler A Abbott Emory University, Georgia
Crawford W Adams, Nashville Tennessee
William A Adams, Chicago Illinois
Malcolm L Allan Vancouver, British Columbia
Arnold S Anderson St Petersburg Florida
Robert J Anderson, Atlanta Georgia
Albert H Andrews, Chicago, Illinois
Norman Arcese Seattle, Washington
J O Armstrong Dallas Texas
Paul W Auston Langdale Alabama
Carl C Aven, Marietta Georgia
Alvan L Barach New York N Y
B Guy Begin Montreal Quebec
Helen C Bernfield Jackson, Mississippi
Otto L Betting, Chicago, Illinois
Katharine R Boucot Philadelphia Pennsylvania
Charles A Brasher, Mt Vernon Missouri
Paul J Breslich Minot, North Dakota
Walter B Brown Livermore California
Donald W Close Indianapolis Indiana
Sumner S Cohen Oak Terrace Minnesota
Lawrence R Coke Winnipeg Manitoba
William S Conklin, Portland Oregon
Winthrop N Davey Ann Arbor Michigan
Everett C Drash Charlottesville Virginia
Seymour M Farber San Francisco California
Max Fleishman Omaha Nebraska
M Jay Flipse, Miami Florida
Carl H Gellenthien Valmora New Mexico
Roy F Goddard Albuquerque New Mexico
Alfred Goldman St Louis Missouri
Burgess L Gordon Albuquerque New Mexico
William P Gray Batesville Arkansas
Albert Guggenheim, Denver Colorado
Joseph M Hanner, San Diego, California
J E J Harris Albuquerque New Mexico
Marvin S Harris Beverly Hills California
W Elliott Harrison Vancouver British Columbia
Thomas G Heaton Toronto Ontario
George R Herrmann Galveston Texas
George H Hobbs Mt Vernon Missouri
Corrin H Hodgson, Rochester Minnesota
Henry R Hoskins San Antonio Texas
W Leonard Howard Northville Michigan
Hollis E Johnson Nashville Tennessee
Francis J Kasheta Glencliff New Hampshire
Ray W Kissane Columbus Ohio
Ross C Kory, Milwaukee, Wisconsin
Alexander Libow, Miami Beach, Florida
Robert C Locke Reno Nevada
Richard V Lynch Clarksburg West Virginia
Arthur M Master New York N Y
Donald W McCauley Okmulgee Oklahoma
Donald R McKay Buffalo New York
Frank A Merlino Providence Rhode Island
Herman J Moersch Rochester Minnesota
Edward H Morgan Seattle Washington
J Arthur Myers Minneapolis, Minnesota
Rush E Netterville Jackson Mississippi
Robert K Oliver Montgomery Alabama
Richard H Overholt Boston Massachusetts
Jerome V Pace Rockville Indiana
J Winthrop Peabody Sr Washington D C
Lloyd E Peckenschneider, Halstead Kansas
Charles K Petter Waukegan, Illinois
Charles Pokorny, Halstead Kansas
Howell S Randolph Phoenix, Arizona
Elmer C Rigby Los Angeles California
William R Rumel Salt Lake City Utah
Paul C Samson Oakland California
J Gordon Seastrunk, Columbia South Carolina
Joseph A Smith, Glen Gardner New Jersey
W B Steen Tucson Arizona
Lawrence H Strug New Orleans Louisiana
James H Stygall Indianapolis Indiana
Darrell H Trumpe, Springfield Illinois
Howard S Van Ordstrand Cleveland Ohio
Raman Viswanathan New Delhi India
William C Voorsanger, San Francisco California
Dean C Walker Tulsa Oklahoma
Buford H Wardrip, San Jose California
Irving Willner Newark New Jersey
W Bernard Yegge Denver, Colorado

Murray Kornfeld Chicago Illinois Executive Director
Ward Bentley, Chicago Illinois Executive Assistant
Harriet L Kruse, Chicago, Illinois Executive Assistant
Margaret Rogers, Chicago Illinois Executive Assistant

The annual meeting of the Board of Regents was held on Wednesday, June 18, and the joint meeting of the Board of Governors and Board of Regents was held at a luncheon on Thursday, June 19 Dr Seymour M Farber, San Francisco, Vice President and Chairman of the Committee on General Arrangements for the meeting, was introduced and welcomed the College Officials to San Francisco Dr Farber and the members of his committees were congratulated on their splendid cooperation in the arrangements for the 24th Annual Meeting

The following reports, resolutions and recommendations were approved by the Board of Regents

Report of the Council on Postgraduate Medical Education

Our council is pleased to announce that five postgraduate courses on diseases of the chest have been presented under the sponsorship of the College during the past 12 months, all of them very well received and well attended The 12th Annual Course was presented in Chicago, October, 1957, with a registration of 53 physicians, the 10th Annual Course in New York City, November, 1957, registration 119, the Third Annual Course in Los Angeles, December, 1957, registration 106, the 11th Annual Course in Philadelphia, March, 1958, registration 58 and one presented in Atlanta in March of 1958, registration 43

This fall our program of postgraduate medical education will start with a special course on cardiopulmonary physiology to be presented as the 13th Annual Postgraduate Course of Chicago during the week of October 13-17 The 11th Annual Postgraduate Course on Diseases of the Chest will be presented in New York City, November 10 through 14, and the 4th Annual California Postgraduate Course on Diseases of the Chest will be presented in San Francisco February 16-20, 1959

J Winthrop Peabody Sr, *Chairman*

Report on College Books

The committee on books wishes to report that the following books sponsored by the American College of Chest Physicians have enjoyed remarkable sales We have prepared this report to indicate the number of books printed, the number of books sold, and the number of each presently available

ROENTGENOLOGY OF THE CHEST, Dr Coleman B Rabin, Chairman, Editorial Committee Charles C Thomas Publishers, Springfield, Illinois April, 1958 3,000 printed—883 sold—2,117 available

CLINICAL CARDIOPULMONARY PHYSIOLOGY, Dr Burgess L Gordon, Chairman, Editorial Committee Grune & Stratton, New York City February, 1957 3,300 printed—3,300 sold—none available

NONTUBERCULOUS DISEASES OF THE CHEST, Dr Andrew L Banyai, Chairman, Editorial Committee Charles C Thomas Publishers, Springfield, Illinois August, 1954 3,152 printed—2,613 sold—539 available

THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS, Dr Edward W Hayes, Sr, Chairman, Editorial Committee Charles C Thomas Publishers, Springfield, Illinois February, 1949 3,094 printed—2,695 sold—399 available

It is gratifying to note that the book on *Clinical Cardiopulmonary Physiology*, which has been on the market only a short time, has been sold out and the committee is now engaged in a complete revision of this book which will be available early in 1959

Upon the request of the publisher, the committee has also authorized a revision of the book on *Nontuberculous Diseases of the Chest* Work on this new book has begun and it is hoped that the book will be available in 1959

Another new book, *Diagnosis and Treatment of Tumors of the Chest*, which is being compiled under the chairmanship of Dr David Spain of New York City, is well under way and we hope to be able to announce its publication early in 1959 The book will be published by Grune & Stratton

Burgess L Gordon, *Chairman*

Report of the Committee on Membership

Between September 1, 1957 and March 1, 1958, 305 applications from all parts of the world were received and presented to the Board of Regents Of these applications, 160 were for Fellowship, 61 for Associate Fellowship, 44 for Associate Membership and 40 for advancement to Fellowship Of this group, 196 applications were filed by physicians in the United States and Canada and 109 by physicians in other countries

Of the total of 305 applications presented to the Board of Regents, 4 were rejected, 2 were tabled and 2 are being held for further investigation Of the 82 physicians in the United States who applied for Fellowship, 14 have been reclassified as Associate Fellows

With the admission of 257 new members in all parts of the world, the total membership of the College is now 6403 As of June 1, 1958, there were 72 applications pending presentation to the Board of Regents at the Interim Session Other applications will, of course, be filed between now and September 1

Chevalier L Jackson, *Chairman*

Report of the Committee on Bronchoesophagology

The study of bronchography conducted by the Committee on Bronchoesophagology was presented at the Annual Meeting of the College in 1957 and was published in DISEASES OF THE CHEST in March, 1958

The committee is presently engaged in the preparation of an editorial entitled "The Role of Endoscopic Photography in the Teaching of Bronchopulmonary Diseases" It is hoped that this editorial will be published in DISEASES OF THE CHEST and that reprints of this article may be sent to the deans of the various medical schools in order to acquaint these schools with the opportunities for visual aids in the teaching of bronchopulmonary disease

At the Interim Meeting of the College in Philadelphia last December, our committee had an informal meeting at the Chevalier Jackson Clinic where we were guests of

Dr Jackson and Dr Norris We had the privilege of witnessing quite a number of bronchoscopic and esophagoscopic examinations and had the opportunity to observe the technics used at the Jackson Clinic, as well as the new instruments We hope to plan a similar informal type of committee meeting at the Interim Session in Rochester this fall

Arthur M Olsen, *Chairman*

BCG Statement

At a Congressional hearing in Washington, D C, certain individuals stressed the use of public funds to support the wider use of BCG vaccination for tuberculosis in the United States In view of the publicity given these hearings, the Executive Council of the College adopted the following statement which, it is hoped, will assist in clarifying the position of the College regarding the use of BCG in the campaign against tuberculosis in the United States

In view of the vital interest in improving public health and welfare, and in the eradication of diseases of the chest in particular, our position regarding the use of BCG (bacillus Calmette-Guerin) against tuberculosis in the United States should be made known At the present time there is insufficient evidence that significant protection is afforded by its use The Council fully endorses the antituberculosis control program of the U S Public Health Service, which includes research in BCG, and urges the continued support of their program

Resolutions

For a number of years, individual members of the College have presented subscriptions for the College journal, DISEASES OF THE CHEST, to their medical fraternities and sororities These subscriptions have proved to be very popular with the members of the fraternities and sororities and it is recommended by the Board of Regents of the College that this program be expanded A resolution was adopted by the Board of Regents recommending that College Chapters be encouraged to present subscriptions for DISEASES OF THE CHEST to the medical fraternities and sororities in their state or district It is hoped that many of the College Chapters will endorse this worthwhile activity

---

WHEREAS, The funds allocated for loan to accepted or acceptable candidates have earmarked approximately 30 per cent of the available funds set aside for resident loan purposes, and

WHEREAS, The nature of the fund shall ultimately become a revolving fund, and thereby it is hoped, be self perpetuating, but will not materialize in this manner until 5 or 6 years have elapsed and loan funds are repaid by the borrowers, together with interest at the rate of 3 per cent per annum, and

WHEREAS, The experience of the committee during the last year would indicate the desirability of accumulating a revolving fund of at least 25,000 dollars for loans to accepted candidates, and

WHEREAS, The anticipated budget of the College would be more satisfactorily adjusted to a small annual contribution rather than to one or more substantial contributions at intervals,

THEREFORE BE IT RESOLVED, That the College shall set up in its annual budget an amount of 2,000 dollars per annum for the resident loan fund until such fund shall reach the total sum of 25,000 dollars

---

WHEREAS, Standards for Fellowship in the American College of Chest Physicians in the United States and Canada have been maintained at a high level by requiring that all candidates for Fellowship hold board certification or successfully complete our oral and written examinations, and

WHEREAS, These standards must be maintained at a high level throughout the world,

THEREFORE BE IT RESOLVED, That all candidates for Fellowship in the College in other countries be required to complete Fellowship examinations unless a waiver of this requirement is granted by the Board of Regents, or request of the Regent or Governor of that country and that such examinations shall be conducted under the supervision of the Regent or Governor of the country or territory concerned, or his appointee, and

BE IT FURTHER RESOLVED, That examinations for Fellowship be established at the earliest date in those countries in which this procedure has not already been adopted

---

WHEREAS, The 25th Annual Meeting of the American College of Chest Physicians will be held in Atlantic City in June of 1959, and

WHEREAS, This Silver Anniversary Meeting will be given special and careful planning to make it the most outstanding meeting in the history of the College,
THEREFORE BE IT RESOLVED, That caps and gowns be worn at the 1959 Convocation of the College in order to lend additional dignity to this important function

WHEREAS, The American College of Chest Physicians will celebrate its Silver Anniversary in 1959, and
WHEREAS, The first meeting of the College was held in Albuquerque, New Mexico, August 10th, 1935, and
WHEREAS, Invitations have been received from the Governor of New Mexico, the Mayor of Albuquerque, and the Presidents of the New Mexico State Medical Society and the Bernalillo County Medical Society to hold a Homecoming Meeting of the College in Albuquerque in 1959,
THEREFORE BE IT RESOLVED, That the American College of Chest Physicians hold its Silver Anniversary Homecoming Meeting in Albuquerque, New Mexico, October, 14-17, 1959

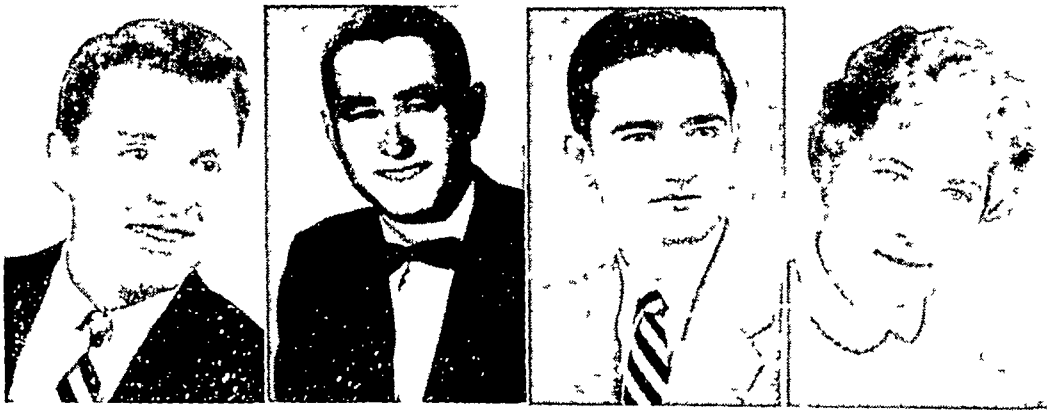
It is recommended that a section on Nuclear Medicine be established to serve under the Committee on Physiologic Therapy of the American College of Chest Physicians

The Board of Regents of the American College of Chest Physicians wishes to express its sincere appreciation to the following people for their efforts and cooperation in making the 24th Annual Meeting of the College a great success
Dr Seymour M Farber and the members of the annual meeting committees
Drs Samuel Bellet and Peter Theodos and the members of their Committee on Scientific Program
Dr Paul H Holinger and the members of the Committee on Motion Pictures
Mrs Seymour M Farber and Mrs Roger Wilson and the members of the Ladies Reception Committee
The Staff of the Fairmont Hotel
The San Francisco Convention and Visitors Bureau
The press and radio station representatives of San Francisco

Gold Medal Awarded by A M A

Drs Collin H Hodgson, J A Callahan, A J Brower and A H Bulbulian of the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, were awarded the Billings Gold Medal for their exhibit on misleading thoracic roentgenograms in the Section on Diseases of the Chest of the American Medical Association meeting in San Francisco, June 23-27

1958 Prize Essay Award Winners



Eugene A Friedberg
University of Buffalo School of Medicine
First Prize

Ronald J O'Reilly
University of California at Los Angeles, School of Medicine
Second Prize

Alan S Deutsch
New York University School of Medicine
Third Prize

June Hagen
University of Cape Town Medical School
Honorable Mention

Report of the Committee on College Essay

The Committee on College Essay is pleased to report that 80 inquiries concerning the 1958 Prize Essay Contest were received from undergraduate medical students in the following countries Argentina (2), Australia, Brazil, Canada (5), Chile, Czechoslovakia (2), England (7), France, India, Iraq, Ireland, Italy (2), Mexico, Nether-

lands, New Zealand, North Ireland, Pakistan, Philippines (2), Scotland, South Africa (2), Switzerland, United States (39), Uruguay, and Yugoslavia (2) Thirty applications for the contest were filed and 23 essays were submitted by students from the following schools

Universidad Nacional Argentina
Sydney University Medical School Australia
University of Alberta Canada
London Hospital Medical College England
B J Medical College, India
Royal College of Medicine Iraq
Queen's University North Ireland
King Edward Medical College Pakistan
Edinburgh University Scotland
University of Cape Town South Africa
University of Geneva Switzerland
United States
Jefferson Medical College (3)
State University of Iowa (2)
University of Minnesota
Georgetown University
State University of New York
University of Virginia
University of California at Los Angeles
University of Buffalo
New York University

First Prize, consisting of $500, was awarded to Eugene A Friedberg for his essay entitled "Murmur Production in Aortic Stenosis An Analysis using a Hydraulic Model" Second Prize, $300, was awarded to Ronald J O'Reilly for his essay on "Clinical Recognition of Carbon Dioxide Intoxication" and Third Prize, $200, was awarded Alan S Deutsch for the essay "Ventricular Septal Defect A Review" The committee awarded Honorable Mention and a prize of $50 to Miss June Hagen for her essay entitled "Cryptococcosis of the Lung"

1959 Essay Contest

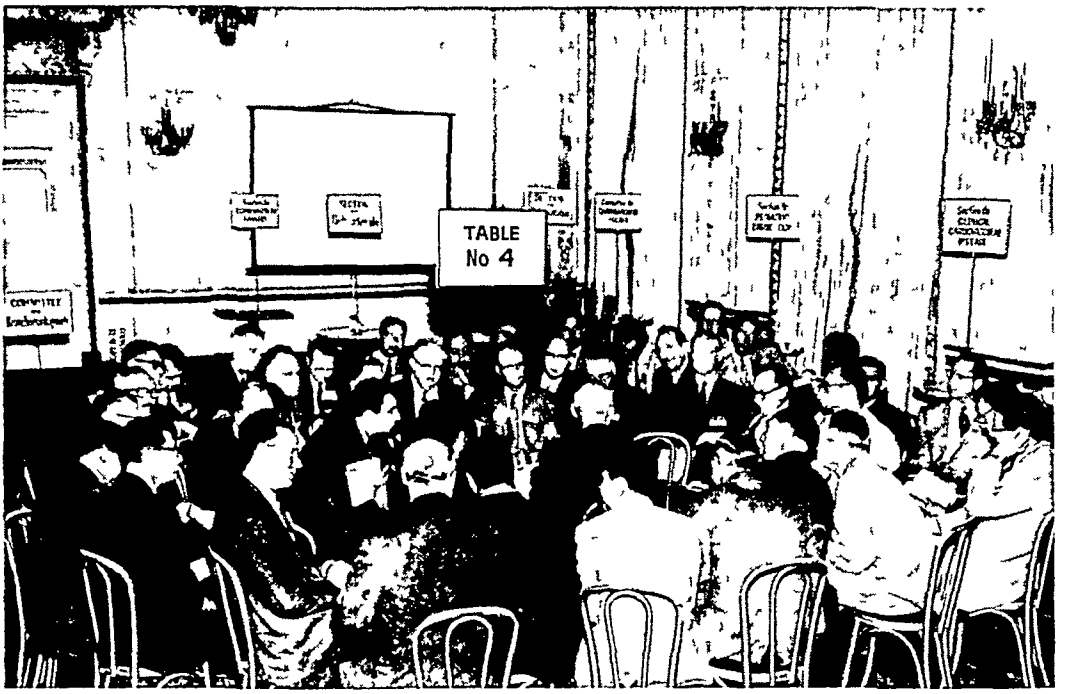
The 1959 Prize Essay Contest is now open to undergraduate medical students throughout the world Awards will be announced at the time of the 25th Annual Meeting of the College in Atlantic City, New Jersey, June 3-7, 1959, in the amounts of $500, $300, and $200 for first, second, and third prizes respectively Each winner will also receive a certificate of merit

The Board of Regents of the College requests the cooperation of members affiliated with medical schools in bringing the contest to the attention of the student body at their schools Essays may be submitted on any phase of medicine or surgery relating to the diagnosis and/or treatment of cardiac or pulmonary diseases The contest will close on April 15, 1959 Applications and instructions for the preparation of manuscripts may be obtained from the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois

Past Presidents of the College Meet in San Francisco

Seated, left to right Dr J Winthrop Peabody, Washington, D C , Dr J Arthur Myers, Minneapolis, Minnesota, Dr James H Stygall, Indianapolis, Indiana, standing, left to right Dr Herman J Moersch, Rochester, Minnesota, Dr Burgess L Gordon, Albuquerque, New Mexico, and Richard H Overholt, Boston, Massachusetts

College Councils and Committees Hold Annual Meetings in San Francisco



A typical committee meeting, Committee on Cardiovascular Diseases under the chairmanship of Dr Arthur M Master, New York City

Fireside Conferences of 24th Annual Meeting

One of the Fireside Conferences held at the San Francisco meeting of the College on Friday, June 20

Board of Governors and Board of Regents Meeting

The annual joint meeting of the Board of Governors and Board of Regents, Fairmont Hotel, San Francisco, Thursday, June 19, 1958

Report of the Treasurer

STATEMENT OF INCOME AND EXPENSES FOR THE YEAR ENDED DECEMBER 31, 1957

INCOME		
Annual Dues		$105,079 41
Fellowship Fees		24,496 50
Sales		
Advertising	$35,349 29	
Subscriptions	30,983 76	
Exhibit Space	2,477 71	
College Services—Net	13,662 50	
	$82,473 26	
Less—Discount Allowed	8,465 15	74,008 11
Interest Received on U S Bonds and Treasury Notes		1,317 45
Interest on Investment in Savings & Loan Associations		1,950 00
TOTAL INCOME		$206,851 47
EXPENSES		
Salaries	$65,161 65	
Printing Journal	55,179 14	
Building Account (Schedule 1)	5,597 93	
Printing and Engraving	8,904 63	
Handling and Posting Journal	6,448 89	
Postage and Shipping	4,276 60	
Translations	300 00	
Officers' and Committee Expense	4,866 13	
Telephone and Telegraph	2,730 00	
Office Expense	2,584 44	
Traveling—Executive Director	1,596 95	
Annual Meeting	7,728 53	
Interim Meeting—Board of Regents	1,568 93	
International Meeting	8,464 99	
Public Relations Expense	1,757 69	
Editorial Board	4,018 75	
Hospital Counselor	1,028 90	
Library Expense	364 30	
Membership Certificates	456 52	
Payroll Taxes	1,026 65	
Prize Essay Award	1,174 74	
Audit	250 00	
Contribution to World Medical Association	500 00	
College Medals	43 95	
Contribution to National Society for Medical Research	25 00	
Depreciation—Furniture and Fixtures	1,668 40	
Total Expenses		187,723 71
NET INCOME		$ 19,127 76

Ralph H Marcus, Certified Public Accountant, Chicago, Illinois

Charles K Petter, *Treasurer*

College Chapter News

MICHIGAN CHAPTER

The Michigan Chapter will meet at the Sheraton-Cadillac Hotel, Detroit, on October 3 Dinner will be served at 6 30 p m, to be followed by the scientific session at 8 00 p m

"Clinical Application of Paper Electrophoreses in Sarcoidosis"
Nathan Levitt, Detroit

"Pulmonary Alveolar Proteinosis"
E Osborne Coates, Jr, Detroit

KENTUCKY CHAPTER

The annual meeting of the Kentucky Chapter will be held at the Brown Hotel, Louisville, September 24 Guest speaker at the dinner meeting commencing at 6 30 p m will be Dr Dwight C McGoon, Rochester, Minnesota who will speak on "The Carcinoid Syndrome Associated with Malignant Bronchial Adenomas" In conjunction with the state medical association meeting, the chapter will present the following program at 2 00 p m

"Lung Abscess"
Daniel Pickar, Louisville

"Pleural Biopsy"
Glover Sanders, Louisville

"Results of Non-operative Treatment of Bronchogenic Carcinoma"
John Paul Stamer, Louisville

"Surgical Treatment of Transposition of the Great Vessels"
Daniel Mahaffey, Houston, Texas

MEXICAN CHAPTER

The Mexican Chapter presented a Symposium on Chronic Cardiopulmonary Disease in conjunction with the National Institute of Cardiology in Mexico City, June 3-4 Prof Dr Ignacio Chavez, Director of the National Institute of Cardiology and an Honorary Fellow of the College, served as moderator Over 600 physicians and medical students attended the symposium

On August 5 the chapter presented the following program at a meeting held in Mexico City

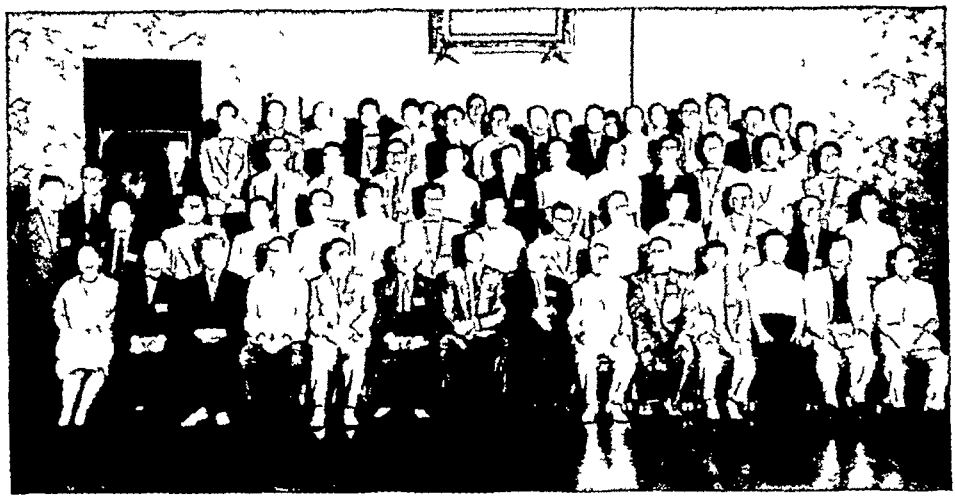
"Pulmonary Eosinophilia"
Raman Viswanathan, Delhi, India

"Surgery of Coarctation of the Aorta"
Fernando Quijano Pitman

The scientific session was followed by a buffet supper in honor of Dr Viswanathan

Lecturers at the Symposium on Chronic Cardiopulmonary Diseases and officers of the Mexican Chapter Left to right, back row Drs Jorge Soni, Fernando Quijano Pitman, Ignacio Chavez, Aradio Lozano Rocha, Isaac Costero, and Pedro Guzzy Center row Drs Donato G Alarcon and Rosario Barroso Front row Drs Victor Rubio, Miguel Jimenez, Rodolfo Limon-Larson, Ismael Cosio-Villegas, and *Enrique Staines*

JAPAN CHAPTER



Members of the Japan Chapter who attended a special meeting in Tokyo, July 26, in honor of the visit to Dr Seymour M Farber, San Francisco, President-Elect of the College Front row, left to right Drs Fumiyo Shimazu, Kingo Shinoi, Chuzo Nagaishi, Masao Tsuzuki, Masanaka Terada, Hiroshige Shiota, Seymour M Farber, Taizo Kumagai, Yoneji Miyagawa, Jo Ono, Osamu Kitamoto, Harutaka Baba, Yoshio Hayashi, and Hirotake Tokugawa

College News Notes

Dr. Andrew L Banyai, Chicago, Illinois, was elected an honorary member of the Sociedad Colombiana de Tisiologia, Bogota, Colombia, and also of the Sociedad Antioquena de Tisiologia y Patologia Toracica, Medellin, Colombia

The Iowa State Tuberculosis Sanatorium at Oakdale is celebrating its 50th anniversary this year **Dr William M Spear** serves as Medical Director and Superintendent and other Fellows of the College on the staff are **Drs Philipp Cahn, Bernhard B Gloeckler,** and **Daniel R Webb**

The honorary degree of Doctor of Laws was conferred upon **Major General Dan C Ogle,** Air Force Surgeon General, on June 8 by his Alma Mater, Eureka College, Eureka, Illinois General Ogle is Governor of the College for the Air Force The degree, the highest honor given by Eureka College, was bestowed upon General Ogle in recognition of his exceptional achievements in his chosen career

Dedication ceremonies for the Jacob J Mendelsohn Laboratory at Fox River Hospital, Batavia, Illinois, were held on June 13 **Dr Otto L Bettag,** Chicago, Director of the Illinois Department of Public Welfare and Regent of the College, delivered an address at the dedication **Dr Mendelsohn,** a Fellow of the College for many years, passed away in 1955 He had served as medical director of the hospital for 29 years

Major General Harry G Armstrong, USAF (MC) was presented the Legion of Merit Award with Second Oak Leaf Cluster recently for exceptionally meritorious conduct in the performance of outstanding service to the United States as Surgeon of the United States Air Forces in Europe from July, 1954 to November, 1957

Dr Charles K Petter, Waukegan, Illinois, was elected President of the Illinois Tuberculosis Association

Dr George L Waldbott, Detroit, Michigan, received first prize for an exhibit on Contact Dermatitis at the Session on Occupational Allergy of the European Academy of Allergy in The Hague, Netherlands recently

Major Khushdeva Singh, Superintendent of the Tuberculosis Centre, Patiala, India, and for many years Secretary of the North India Chapter of the College, was awarded the honor of "Padam Shri" by the Government of India for his

outstanding work in the field of tuberculosis and diseases of the chest The honor was conferred by the President of the Government of India at Government House in New Delhi

Dr Francis J Weber, Washington, D C, has been appointed Chief of the newly established Division of Radiological Health of the Public Health Service

Dr Jethro Gough, Cardiff, Wales, recently lectured at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota on the subject "Some Recent Investigations in Pulmonary Pathology"

Dr Harry Golembe, Liberty, New York, has been elected Vice-President of the Medical Society of the State of New York

Colonel Weldon J Walker was a guest speaker at the Eighth Middle East Medical Assembly held May 9-11 at the American University in Beirut, Lebanon Colonel Walker presented papers entitled "Newer Concepts Concerning the Cause and Prevention of Hypertension" and "The Lipid Problem in Atherosclerosis"

Announcements

We are pleased to report that the book, CLINICAL CARDIOPULMONARY PHYSIOLOGY, edited by Dr Burgess L Gordon and sponsored by the American College of Chest Physicians, has enjoyed such a large sale that stock on this book is now entirely depleted It is requested that orders for this book be withheld until the announcement of a new revised edition which is now being prepared by the College Release of this revised edition is anticipated early in 1959

The next Postgraduate Course in Laryngology and Bronchoesophagology to be presented by the University of Illinois College of Medicine is scheduled for October 27-November 8, 1958 The course is under the direction of Dr Paul H Holinger Interested registrants may write directly to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois

---

A three-day postgraduate course on cardiopulmonary diseases will be held in Denver, Colorado, October 16-18, 1958, under the sponsorship of the Colorado Chapter of the American College of Chest Physicians, Colorado Heart Study Group, Fitzsimons Army Hospital, National Jewish Hospital, and the University of Colorado School of Medicine. Outstanding speakers will lecture at this postgraduate course For further information, please communicate with the Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Street, Denver, Colorado

Special Postgraduate Course

CLINICAL CARDIOPULMONARY PHYSIOLOGY

Edgewater Beach Hotel, Chicago, Illinois

October 13-17, 1958

Have you received your copy of the program for this special postgraduate course? If you are interested in attending this course, please write to the Executive Offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, for a copy of the program

Enrollment is limited.

Applications will be accepted in the order received.

DISEASES of the CHEST

VOLUME XXXIV OCTOBER, 1958 NUMBER 4

Uncommon Roentgen Patterns of Pulmonary Sarcoidosis*

BENJAMIN FELSON, M D , F C C P

Cincinnati, Ohio

The common roentgen features of intrathoracic sarcoidosis have been adequately described and clearly depicted in the literature Numerous reports illustrate the variegated manifestations of the disease the lymph node enlargement, the disseminated miliary densities, the localized infiltrates, and the fibrotic changes, alone or in combination

However, not all cases reveal these more or less typical findings The present report deals with two interesting but less familiar roentgen patterns of pulmonary sarcoidosis which may, at times, bring this disease to mind—the multinodular and the multicystic

THE MULTINODULAR PATTERN

This relatively uncommon form of sarcoidosis has received little mention in the literature, only a few cases having been recorded McCord and Hyman,[1] in 1952, reported and illustrated two cases of pulmonary sarcoidosis in which large parenchymal nodules, indistinguishable from the "snowball" lesions of metastatic malignancy, were demonstrated roentgenographically Turiaf and Brun,[2] in their monograph on sarcoidosis, reproduced the roentgenograms of another case There were five large rather well-demarcated nodules, one in the right apex and the others in the lower lung fields The chest was otherwise normal Two months later the lesions had almost disappeared A chest film three years earlier was said to have shown only disseminated miliary densities

I have had the opportunity of studying the roentgenograms in five cases, including the two reported by McCord and Hyman In four instances a roentgen diagnosis of malignant pulmonary metastases was originally made However, the mild clinical symptoms and the continued well-being of the patients led to further study, and ultimately microscopic evidence of sarcoid was obtained, twice from the lung and twice from a peripheral lymph node In the fifth case, reported below, sarcoid was suspected clinically and roentgenologically and the diagnosis was confirmed by scalene

*From the Department of Radiology, University of Cincinnati College of Medicine, and the Cincinnati General Hospital

Copyright 1958 by the American College of Chest Physicians

lymph node biopsy Four of the five patients were young Negroes and the fifth was a Negress, age 26 All were mildly ill, with general symptoms, such as fever, malaise, night sweats, and weight loss, and respiratory symptoms, such as cough, dyspnea, and expectoration All but one of the cases showed peripheral lymph node enlargement of slight to moderate degree, and two showed elevation of the serum globulin and serum calcium No other clinical evidence of systemic sarcoidosis was apparent

Roentgen Findings In each case the chest roentgenogram revealed changes far out of proportion to the mild clinical manifestations There were numerous round or oval lesions, 5 to 40 mm in diameter, widely distributed in the lungs In four of the cases the nodules appeared to be more numerous in the central zones, where they tended to be confluent The individual nodules in these four cases presented a hazy or fluffy outline, the "soft" margin sometimes appearing as a halo around the central density The confluence of the nodules and their lack of sharp borders did not closely simulate the common type of metastases, but the resemblance to the "halo" nodules of chorionepithelioma, also seen occasionally with other metastatic tumors, was striking The fifth case showed scattered sharply-outlined nodules varying from about 5 to 15 mm in diameter, in no way different from the appearance of the garden variety of pulmonary metastases

In three of the cases the superior mediastinum appeared widened, presumably due to lymph node enlargement In only one was hilar lymph node enlargement apparent, but in three others the overlying pulmonary lesions obscured the hilar areas

Follow-up films were obtained in all but the patient with the sharply circumscribed nodules In one, followed for five months, no change was

FIGURE 1A FIGURE 1B

Figure 1 (Case 1) Multinodular sarcoidosis A August 4, 1957 There are numerous large round and oval coalescent lesions widely distributed in the lungs The nodules have fluffy margins, giving them a halo-like outline There is superior mediastinal and left hilar lymph node enlargement B August 16, 1957 The nodular densities are distinctly smaller and somewhat less dense

observed In another, slight improvement was noted at four months One case, previously reported,[3] showed a striking change at 10 months, with marked resolution of the large nodules and the superimposition of a fine diffuse miliary pattern In the following case definite improvement was evident in 12 days and considerable regression was noted at five months

Case Report

Case 1 (Reported through the courtesy of Drs I Leonard Bernstein and Paul F Fletcher) A P, a 26 year old colored woman, was first admitted to Jewish Hospital, Cincinnati, in October, 1955, in labor She delivered a normal full-term infant A 70 mm photofluorographic chest film appeared normal In May, 1956, another routine photofluorographic chest film was normal

On August 3, 1957, she was re-admitted because of a dry non-productive cough, intermittent fever, night sweats, and a weight loss of five pounds The cough had been present for five months, but the other symptoms were of more recent origin She was not acutely ill, and had no fever on admission Physical examination was normal except for fine rales and inspiratory wheezes at the lung bases

Blood counts and smear were normal except for an eosinophilia of 9 per cent, which soon fell to normal The sedimentation rate was 34 mm No sputum was expectorated The serum albumin, globulin, and calcium levels were normal, as were all other laboratory studies Skin tests with tuberculin (second strength) and histoplasmin were negative Biopsy of a scalene lymph node revealed the histological picture of sarcoid Pulmonary function studies were interpreted as indicating a restrictive process, compatible with the clinical diagnosis of sarcoidosis

The chest roentgenogram on August 4 (Fig 1A) revealed numerous large round and oval coalescent lesions, 1 to 4 cm in diameter, widely distributed throughout both lungs The margins of the nodules were ill-defined and fluffy There was widening of the superior mediastinum and a nodular prominence in the left hilum thought to represent enlarged lymph nodes On August 16 the chest film showed moderate improvement, many of the nodules appearing distinctly smaller (Fig 1B)

FIGURE 2 There are large and small bullae in the right apex and small ones in the left The hila and superior mediastinum are widened and somewhat lobulated in outline

FIGURE 3A FIGURE 3B FIGURE 3C

Figure 3 (Courtesy of Dr Lee S Rosenberg) A January, 1944 Diffuse miliary nodulation, marked tracheobronchial lymph node enlargement B December, 1952 Innumerable small round radiolucencies are now present in the upper two-thirds of both lungs The lymph node enlargement is still quite striking Residual lipiodol is present in the lungs C Bronchogram There is extensive cystic bronchiectasis In the upper lobes the bronchi are crowded together

She improved promptly on steroids and was discharged, symptom-free, on August 19, 1957 She has remained clinically well since that time Chest roentgenograms in March, 1958, showed about 75 per cent regression in the size of the pulmonary nodules and the hilar and mediastinal enlargement had almost completely disappeared

Comment

The multinodular roentgen pattern described above cannot, of course, be considered diagnostic of sarcoidosis It is a rare manifestation of this disease and perhaps would more often result from tumor metastases or pulmonary lymphoma Multiple histoplasmomas, the nodular form of tuberculosis, and multiple benign tumors (e g hamartomas) must also be considered in differential diagnosis, but in these conditions the nodules are fewer in number and sharper in outline, and often some of them contain calcium [3]

Certain features encountered in the present group of cases should provide the clue to the correct diagnosis These include the mild clinical symptoms and the continued well-being of the patients, the presence in other body systems of stigmata consistent with sarcoidosis, especially lymphadenopathy, the apparent predilection for young Negroes, the fluffy margins of the pulmonary nodules and their tendency to become confluent, and the stationary or even regressive course shown roentgenographically

THE MULTICYSTIC PATTERN

The multicystic pattern of sarcoidosis is probably a complication of the irreversible fibrotic stage of the disease It is not infrequently encountered at the autopsy table in patients dying of sarcoidosis but has seldom been emphasized as a prominent or predominant roentgen manifestation of the disease Individual cases have been reported and occasional examples have been included in articles dealing with the roentgen manifestations of sarcoid,[4 16] but few authors have dwelt on this phase of the disease

Longcope and Freiman,[6] in their classical monograph on sarcoidosis, stated that the large cavitary lesions seen on roentgenograms usually proved to be emphysematous bullae or cystic bronchiectatic dilatations They pointed out that the emphysema resulted from extensive diffuse pulmonary fibrosis, and that when such changes were demonstrable complete regression was no longer possible

In their monograph on intrathoracic sarcoidosis, Turiaf and Brun[2] devoted considerable discussion to this subject and illustrated local and widespread forms of bullous emphysema as well as a reversible type They noted a good correlation between the extent of the emphysema and the severity of the symptoms and signs, and recorded such complications as pneumothorax, fluid levels from secondary infection, and cor pulmonale

Mallory[11] reported the autopsy findings of six patients who died of extensive long-standing pulmonary fibrosis He noted widespread coarse emphysema, with bullae ranging up to a centimeter in diameter in all the cases Microscopically, numerous non-caseating miliary tubercles were also present He considered it probable that these cases were examples of sarcoidosis

FIG 4A

FIG 4B

FIG 4C

Figure 4 (Case 2) A January, 1954 Infiltrate is present in both upper lobes and both hila are elevated The right hilum is enlarged B November, 1956 Moderately large bullae (arrows) have replaced much of the infiltrate The trachea is deviated to the right Bilateral hila and mediastinal enlargement is present C Lordotic view shows the emphysematous bullae and lymph node enlargement to better advantage

Our experience with the multicystic pattern of sarcoidosis dates back about 10 years and is based on nine proved cases Six were seen at the Cincinnati General Hospital and represent 21 per cent of the 28 proved cases of sarcoid at this institution in which chest roentgenograms were available The remaining three cases came from other institutions in the Cincinnati area

All six cases from the General Hospital were Negro (Negroes account for about 50 per cent of the hospital admissions) but the three outside cases were white There were five women and four men in the group The ages ranged from 29 to 63 years, with an average of 38 years Comparable figures for the control group of 22 cases of sarcoid from the General Hospital who did not show the multicystic pattern were as follows 22 Negro, 0 white, 18 women, 4 men, age range 19 to 49 with an average of 31 years, seven years less than that of the multicystic group

Of the nine multicystic cases, eight had chronic cough and five had hemoptysis Dyspnea and expectoration were prominent symptoms, but weight loss was infrequent Two had recurrent episodes of acute pneumonia Only one, a patient with relatively minimal pulmonary changes, was asymptomatic Evidence of cor pulmonale was present in three of the multicystic and in none of the control cases The incidence of involvement of the skin, peripheral lymph nodes, liver, spleen, eyes, salivary glands, and bones in the cystic cases was approximately the same as in the control group Renal calculi were encountered once in each group, and abnormal levels of serum calcium and serum proteins also occurred with equal frequency in the two groups

Five of the nine multicystic cases died, and autopsy was performed in three In each, widespread pulmonary and pleural fibrosis were found, associated with bullous emphysema and bronchiectasis In two, miliary granulomas consistent with sarcoid were found microscopically in the lung and other viscera In the third, no evidence of sarcoid was demonstrated at autopsy, although several years earlier the diagnosis had been established by clinical, roentgen, and histologic findings

Roentgen Findings On the initial roentgenogram multicystic lesions were the predominant feature in only one case, although they were present to some degree in several others In the remaining eight, extensive pulmonary infiltrate was apparent, fibrotic in nature in six and miliary in two In two cases, one with fibrosis and one with miliary densities, the involvement was limited to one lung The unilateral miliary lesions exemplified an exceedingly rare distribution of this form of sarcoidosis Mediastinal and/or hilar enlargement was evident on the first film in seven cases and appeared later in one Spontaneous pneumothorax occurred terminally in one case

Two cases were followed roentgenologically for less than six months In the other seven, chest films were available for a period of from three to nine years In these, once the cystic lesions appeared, they increased slowly in number and extent In no instance did regression occur, instead, there was gradual progression with partial transformation of the fibrotic

process into cystic lesions In one of the two cases presenting a miliary pattern, this was subsequently replaced by fibrosis before the bullae developed

The ultimate appearance was often quite characteristic (Figs 2, 3, and 4) There was widespread involvement of the lungs with strand-like or ill-defined densities honeycombed with large or small thin-walled cavities having the typical appearance of bullae in seven cases and of cystic bronchiectasis in two In addition—and an important part of the picture—there was definite enlargement of the hila and/or the superior mediastinum The margins of the broadened mediastinum lacked the usual sharp definition seen in the earlier stages of sarcoidosis because the adjacent pulmonary lesions overlapped and obscured them to some degree

In two cases bronchograms were obtained late in the course of the disease Both revealed moderately extensive cystic bronchiectasis, in addition, one showed crowding of the bronchi in the upper lobes, indicating collapse or fibrosis (Fig 3)

In the differential diagnosis any condition which causes widespead pulmonary fibrosis which, in turn, results in bullous emphysema or cystic bronchiectasis, must receive consideration Many diseases fall into this category,[17] including tuberculosis, histoplasmosis, diffuse interstitial fibrosis of Hamman and Rich, scleroderma, bronchiectasis, progressive bullous emphysema or "vanishing lung," pneumoconiosis, and the later stages of chronic bronchial asthma These conditions often closely simulate multicystic sarcoidosis roentgenologically as well as clinically However, the enlarged tracheobronchial nodes, earlier chest roentgenograms showing the more typical appearance of sarcoid, and the presence of other clinical and laboratory evidence consistent with sarcoidosis suggested the correct diagnosis in a number of the cases in the present series

Case 2 S O, a 31 year old colored woman, was admitted to Cincinnati General Hospital October 29, 1956, with a history of dyspnea, cough, and expectoration associated with bouts of fever Past history revealed that she had been a patient in a tuberculosis sanatorium rather briefly in 1954 and again in 1957 with similar complaints A diagnosis of pulmonary tuberculosis had been made but sputums were repeatedly negative On the present admission physical examination revealed moderate respiratory distress, evidence of weight loss, bilateral inspiratory rales over the apices, and dullness and decreased fremitus over the right lung

A chest film (Fig 4B) showed infiltrate in both upper lobes, in which thin-walled radiolucencies having the appearance of bullae were apparent The hilar shadows were elevated and enlarged and the superior mediastinum was slightly widened The cardiac contours were obliterated by adjacent pulmonary involvement A roentgen impression of tuberculosis or sarcoidosis was made The 1954 films from the sanatorium were obtained (Fig 4A) and revealed the infiltrate in both upper lobes and right hilar enlargement Bullae were not evident

Multiple sputum examinations were negative for tubercle bacilli and fungi The electrocardiogram revealed right ventricular hypertrophy The serum calcium and the serum albumin and globulin were normal There was considerable respiratory impairment shown by pulmonary function studies Biopsy of a scalene node showed miliary non-caseating granulomas, consistent with sarcoid She was discharged December 8, somewhat improved symptomatically She was readmitted on December 23 for cardiac catheterization Following this procedure she became nauseated and apprehensive, and complained of right chest and shoulder pain Her blood pressure fell, she responded poorly to emergency care, and died two days later

Autopsy revealed large conglomerations of lymph nodes in the mediastinum Pleural effusions were present bilaterally but the pleural surfaces appeared normal The right

lung weighed 500 grams and the left 360 Numerous bullae were seen throughout the lungs On cut section the lung parenchyma appeared markedly fibrotic and honeycombed The bronchioli were quite prominent The right ventricle was dilated and its wall thickened There was thrombosis of the right atrial appendage No other significant finding was noted

Microscopically, the lungs showed distortion of the parenchyma with marked interstitial pneumonitis of nonspecific nature and striking fibrosis of the alveolar septa In the walls of the small and large bronchi there was much scarring, and many giant cells containing large Schaumann bodies were seen Scattered non-caseating granulomas were present in the lungs, lymph nodes, heart, spleen, and liver Final diagnoses were sarcoidosis, pulmonary fibrosis, bullous emphysema, bronchiectasis, cor pulmonale, and thrombosis of the right atrial appendage

Comment

The seriousness of the multicystic form of pulmonary sarcoidosis is evident when it is pointed out that five of the nine cases have died and that two others were doing poorly when last seen One did well but was followed for only a month The other had moderate symptoms five years after bullae first became evident The causes of death in the five cases were respiratory insufficiency and/or *cor pulmonale* in four, and tension pneumothorax in one

The sequential roentgenograms appear to substantiate the viewpoint that the cystic changes result from pulmonary fibrosis While it is realized that the roentgen recognition of fibrosis is not always reliable, the criteria used in the present cases seem adequate These included strand-like densities, persistence of the shadows for periods in excess of a year, and retraction of fissures, hila, and mediastinal structures

It is, of course, realized that there is no microscopic picture which is pathognomonic for the diagnosis of sarcoid [11] However, the presence of compatible clinical and roentgen findings, when added to the demonstration of non-caseating granulomas, leaves little doubt that these patients suffered from sarcoidosis It is also apparent that the multicystic pattern represents a late manifestation of this disease

SUMMARY

The present report deals with two interesting but less familiar roentgen patterns of pulmonary sarcoidosis, the multinodular and multicystic The former consists of multiple large nodules simulating those of malignant pulmonary metastases The multicystic type is probably a complication of the fibrotic stage of sarcoidosis, the cysts representing emphysematous bullae and bronchiectatic cavities The clinical and roentgen features encountered in a group of five cases presenting the multinodular and nine cases showing the multicystic pattern are described and their importance in differential diagnosis emphasized Criteria are set forth which should suggest the diagnosis of sarcoidosis in such cases

---

Acknowledgments The author wishes to thank Drs Helen Ackerman, I Leonard Bernstein, Paul F Fletcher, Hans Plaut, and Lee S Rosenberg for permission to include their cases, and to Drs Rosenberg and David G Freiman for reviewing the manuscript

RESUMEN

Esta comunicacion se refiere a dos aspectos radiológicos interesantes pero menos comunes de la sarcoidosis pulmonar, la forma multinodular y poliquística La primera consiste en grandes nódulos numerosos que simulan los de las metástasis pulmonares La forma poliquística en una complicacion probable de la etapa fibrosa de la sarcoidosis, siendo los quistes bulas enfisematosas y cavidades bronquiectasicas Las características clínicas y radiológicas encontradas en este grupo de cinco casos que presentan el aspecto multinodular y nueve casos de forma poliquística se describen de acuerdo con su importancia y se recalca el diagnóstico diferencial

Se establecen criterios que sugerirían el diagnóstico de sarcoidosis en tales casos

RESUME

La présente communication se rapporte à deux images radiologiques de sarcoidose pulmonaire intéressantes, mais peu communes, l'aspect multinodulaire et multikystique Le premier consiste en nodules multiples étendus, simulant ceux des métastases pulmonaires malignes La forme multikystique est probablement une complication de l'état fibreux de la sarcoidose, les kystes représentant des bulles emphysémateuses et des cavités bronchiectasiques L'auteur décrit les caractères cliniques et radiologiques rencontrés dans un groupe de cinq cas présentant la forme multinodulaire, et neuf cas montrant un aspect multikystique, et il met en lumière leur importance dans le diagnostic différentiel Il propose des critères qui permettraient d'evoquer le diagnostic de sarcoidose dans de tels cas

ZUSAMMENFASSUNG

Die vorliegende Mitteilung berichtet uber 2 interessante, jedoch weniger bekannte rontgenologische Erscheinungsformen der pulmonalen Sarkoidose, namlich die multinodulare und die multizystische Form Die erstgenannte besteht aus multiplen grossen Knoten, die maligne pulmonale Metastasen vortauschen Der multizystische Typ ist wahrscheinlich eine Komplikation des fibrotischen Stadiums der Sarkoidose, wobei die Zysten Emphysemblaschen und bronchiektatische Kavernen darstellen Es werden die klinischen und rontgenologischen Eigenschaften beschrieben, die in je einer Gruppe von 5 Fallen des multinodularen und 9 des multizystischen Typs angetroffen werden, und ihre Bedeutung in differentialdiagnostischer Hinsicht wird hervorgehoben Es werden Kriterien aufgezeigt, die die Diagnose eines Sarkoids in solchen Fallen nahe legen

REFERENCES

1 McCord, M C and Hyman, H L "Pulmonary Sarcoidosis with the Roentgenologic Appearance of Metastatic Neoplasm A Report of Two Cases," *Amer J Roentg and Rad Ther*, 67 259, 1952

2 Turiaf, E and Brun, J *La Sarcoidose Endothoracique de Besnier-Boeck-Schaumann Localisations mediastino-pulmonaires et bronchiques Atteintes cardiaques*, Paris, 1955, Expansion Scient Franc

3 Felson, B "Less Familiar Roentgen Patterns of Pulmonary Granulomas Sarcoidosis, Histoplasmosis, and Non-infectious Granulomatosis (Wegener's Syndrome)," *Amer J of Roentg Rad Ther and Nuc Med*, to be published

4 "Cabot Case Number 36041," *New England J Med*, 242 149, 1950

5 Hogan, G F "Sarcoidosis A Report of Five Cases with One Autopsy," *Am Rev Tuberc*, 54 166, 1946

6 Longcope, W T and Freiman, D G *A Study of Sarcoidosis*, Baltimore, 1952, Williams and Wilkins

7 Ustvedt, H J "Autopsy Findings in Boeck's Sarcoid," *Tubercle*, 29 107, 1948

8 Brun, J and Viallier, J "Maladie de Besnier-Boeck-Schaumann avec atteintes pulmonaires pseudo-kystiques," *J franc med et chir thorac*, 2 273, 1948

9 Mitchum, W R and Brady, B M "Differential Diagnosis of Fibrosing Lung Lesions," *Radiology*, 68 36, 1957

10 Volutet, G, Rabinowicz, T and Grassett, E "Forme bronchectasique de la maladie de Besnier-Boeck," *J Radiol and Electrol*, 34 818, 1953

11 Malloy, T B "Pathology of Pulmonary Fibrosis, including Chronic Pulmonary Sarcoidosis," *Radiology*, 51 468, 1948

12 Nittet, L *Changes in the Chest Roentgenogram in Boeck's Sarcoid of the Lungs*, Supplem No 105, Stockholm, 1953, Acta Radiologica

13 Reisner, D "Boeck's Sarcoid and Systemic Sarcoidosis," *Amer Rev Tuberc*, 49 289, 1944

14 Scadding, J G "Sarcoidosis, with Special Reference to Lung Changes," *Brit Med J*, 1 745, 1950

15 Banyai, A L, Editorial "Pulmonary Sarcoidosis," *Dis Chest*, 18 254, 1950

16 Appelman, A C *Nederl tijdschr v geneesk*, 91 2985, 1947 Quoted by Laforet and Laforet[17]

17 Laforet, E G and Laforet, M T "Non-tuberculous Cavitary Disease of the Lungs," *Dis Chest*, 31 665, 1957

A Characterization of Atypical Acid-Fast Bacilli Obtained from Patients with Pulmonary Tuberculosis*, **

HAROLD KELTZ, M D, ROSEMARY COLTON, and WILLIAM LESTER, M D, F C C P

Hinsdale, Illinois

Introduction

The increasing use of simple and effective cultural techniques for the isolation of tubercle bacilli has been most valuable in confirming the diagnosis of tuberculosis and evaluating the activity of the disease in any given patient However, as a by-product of this increasing reliance upon the cultural isolation of tubercle bacilli from sputum, gastric contents, or other secretions, more frequent reports are appearing concerning the isolation of atypical acid-fast bacilli from such sources [1-10] In many instances it is difficult to assess the etiologic relationship of such atypical organisms to the disease encountered in the patient from which they originated [1-11] However, it is essential that these organisms are properly characterized so that diagnosis can be made and, when indicated, chemotherapy can be initiated or continued

Upon reviewing 649 culture-positive, consecutive cases, studied diagnostically in our laboratory from February, 1955, to November, 1956, we found that 164 patients had cultures reported positive for atypical acid-fast bacilli at one time or another This was an incidence of slightly more than 25 per cent The atypical cultures obtained in this series had been stored and they formed the basis of this report which details the results of our efforts to characterize these organisms and to relate the findings to the clinical disease found in the patients

Materials and Methods

The ultimate basis for judging a culture to be atypical was made upon a careful inspection of colonial morphology It was immediately apparent that the 164 atypical strains isolated from our patients fell in three groups which generally conformed to those described by the "Cooperative Study of Mycobacteria" [12] For purposes of clarity the three groups may be differentiated as follows

Group I Photochromogenic strains These form a lemon yellow pigment during growth if exposed to light This group comprised 22 6 per cent of our atypical cultures isolated from patients

This investigation was supported (in part) by Research Grant E 1174 from The National Institute of Allergy and Infectious Diseases, Public Health Service

Suburban Cook County Tuberculosis Sanitarium District, Hospital-Sanitarium

*Presented in part before the Sixteenth Veterans Administration-Armed Forces Conference on The Chemotherapy of Tuberculosis, St Louis, Missouri, February 12, 1957

**Presented before the Medical Session as part of Section 2B at the Annual Meeting of the National Tuberculosis Association, Kansas City Missouri, May 7, 1957

TABLE IA

SUMMARY OF DATA OBTAINED FROM TYPICAL AND ATYPICAL CULTURES

		Cellular Morphology			Reduction of Dyes[3]				
A Typical Cultures	Medium of Primary Isolation[1]	Cording[2]	Average Bacillary Length in Micra	Granules	Sodium Dibromoindophenol	Indophenol	Neutral Red Test	Catalase Reaction	Clinical Status
1 (L Z)	B	+	3 0	0	0	0	+	+	Min
3 (E M)	B	+	3 0	0	0	0	+	+	Min
5 (E J)	L	+	2 0	0	0	0	+	+	Mod Adv
10 (I C)	B	+	2 5	0	0	0	+	±	Min
11 (H H)	A A	+	3 0	0	0	0	+	+	Far Adv
15 (C P)	B	+	2 5	0	0	0	+	+	Far Adv
21 (P G)	L	+	3 0	0	0	0	+	±	Fair Adv
22 (R R)	B	+	3 0	0	+	+	+	+	Fair Adv
26 (I R)	L	+	3 5	+	0	0	+	+	Far Adv
28 (R R)	B	+	3 5	+	0	0	+	+	Far Adv
32 (E L)	A A	+	3 0	+	0	0	+	+	Far Adv
B Group I Cultures									
6 (H S)	L	0	2 0	+	+	+	—	++	Far Adv
7 (E M)	B	±	2 0	+	0	0	—	++	Min
9 (E K)	L	0	3 0	+	+	+	—	++	Fair Adv
13 (F T)	A A	+	2 0	+	++	++	—	++	Mod Adv
14 (E E)	L	0	2 0	+	++	+	—	++	Far Adv
17 (R C)	L	±	2 5	0	++	++	—	++	Mod Adv
24 (H N)	L	±	1 5	+	++	++	—	++	Far Adv
27 (S H)	B	±	10 0	+	++	++	—	++	Mod Adv
29 (W N)	A A	±	2 5	+	++	++	—	++	Fair Adv
30 (R B)	L	+	3 0	+	0	++	—	++	Far Adv
34 (D K)	A A	0	3 0	+	++	+	—	++	Min
36 (G S)	B	+	2 5	+	++	++	—	++	Min

[1] B = Tarshis Blood Medium, L = Lowenstein Medium, A A = Modified Dubos Albumin Agar Medium

[2] + = Definite Cording, ± = Partial Cording, 0 = No Cording

[3] 0 = No Reduction, + = Partial Reduction, ++ = Complete Reduction

Group II Non-photochromic strains These are white, beige, or buff to yellowish, the pigmentation, if any, is not light conditioned This group comprised 2 4 per cent of the atypical cultures isolated

Group III Deeply chromogenic yellow-orange strains which are pigmented even in complete darkness (skotochromogenic) This group comprised 75 per cent of the atypical cultures isolated

Twenty-five cultures of atypical acid-fast bacilli were selected for detailed study and they included 12 strains of Group I, three of Group II, and 10 of Group III They were compared in all respects with 11 cultures of typical human type tubercle bacilli All cultures which were used for this study were isolated from one of the following diagnostic media routinely used in this laboratory (1) Lowenstein (Jensen Holm Modification),[11] (2) Blood Medium,[11] and (3) Modified Dubos Albumin Agar Medium [13] The specific characteristics which we studied consisted of the following (1) Colonial morphology, (2) Cellular morphology, (3) Rate of growth in liquid medium, (4) Oxidation-Reduction of dyes, (5) Neutral red test, (6) Catalase reaction, (7) Drug sensitivity, (8) Guinea pig virulence, (9) Clinical course in humans, and (10) Correlation between histopathology and bacteriology of resected specimens whenever available

Initially, a loopful of each culture, obtained from growth on solid medium, was transferred into a tube containing 5 ml of Dubos Tween 80 liquid medium[16] and triturated These liquid cultures were incubated at 37° C for seven days and all sub cultures were made subsequently from them All cultures were coded by numbers which were assigned blindly and their source was not divulged until the tests were completed

1 *Colonial Morphology*

Growth on Lowenstein medium was used for the analysis of colony character and pigmentation For this purpose, inocula consisting of single loopfuls of seven day liquid Dubos cultures were placed on individual Lowenstein plates and these were incubated for 21 days in the dark and

Footnote

		Heat to dissolve and add	
		Dist water	750 ml
Basal Medium	800 ml[14]	Casein digest	2 0 gm
$K H_2 PO_4$	1 0 gm	$Fe NH_4$ Citrate	0 05 gm
$Na_2 H PO_4 \cdot 12 H_2O$	6 3 gm	$Mg SO_4 \cdot 3 H_2O$	0 006 gm
Asparagine	2 0 gm	Ca Cl	0 0005 gm
Dist water	100 00 ml	$Zn SO_4$	0 0001 gm
		$Cu SO_4$	0 0001 gm

Adjust pH to 6 5-6 8 and add
Agar 20 0 gm
Green vegetable coloring 0 1 ml
Autoclave 15 minutes at 20#
Add aseptically to Agar base cooled to 50° C
Bovine Albumin Fraction V—10 gm
(200 ml of 5% solution of albumin in 2% saline, neutralized, inactivated at 56° C for ½ hour and sterilized by filtration through a Seitz filter)
Glucose—10 gm
(20 ml of an autoclaved 50% solution)
Penicillin—5000 units in sterile distilled water
Tube aseptically

then inspected All cultures were left in the light at room temperature for 24 hours and then re-examined for the acquisition of or changes in pigment Colonial morphology was noted in every instance

2 *Cellular Morphology*

Sub-cultures of each strain in Dubos Tween 80 medium were prepared and their growth was carefully observed photelometrically When maximum rate of growth was obtained, smears were made and stained with modified Kinyoun Stain [1-*] The stained smears were carefully examined and the appearance of the individual cells characterized and their size measured The presence or absence of granules and tendency to cord were noted

TABLE IB

SUMMARY OF DATA OBTAINED FROM TYPICAL AND ATYPICAL CULTURES

		Cellular Morphology			Reduction of Dyes[3]				
C Group II Cultures	Medium of Primary Isolation[1]	Cording[2]	Average Bacillary Length in Microns	Granules	Sodium Dibromoindophenol	Indophenol	Neutral Red Test	Catalase Reaction	Clinical Status
2 (T H)	B	0	2 0	0	+	+	—	+	Far Adv
4 (S M)	B	±	2 0	0	+	++	—	++	Far Adv
18 (E M)	A A	±	3 5	0	+	0	—	++	Mod Adv
D Group III									
8 (F K)	B	0	1 5	+	++	+	+	++	Far Adv
12 (S Z)	B	0	1 5	+	++	++	—	++	Mod Adv
14 (G O)	B	0	2 0	+	+	+	—	++	Mod Adv
16 (J K)	A A	0	1 5	+	+	++	+	++	Far Adv
20 (J K)	L	0	2 0	+	+	+	+	++	Far Adv
23 (R S)	L	0	2 0	+	++	++	—	++	Far Adv
25 (I R)	L	±	1 5	+	++	++	—	+	Far Adv
31 (D C)	L	±	1 5	+	+	+	—	++	Min
33 (R Y)	L	0	3 0	+	++	+	—	++	Min
35 (G B)	L	0	1 5	+	+	0	—	++	? Tbc

[1] B = Harshis Blood Medium, L = Lowenstein Medium, A A = Modified Dubos Albumin Agar Medium

[2] + = Definite Cording ± = Partial Cording 0 = No Cording

[3] 0 = No Reduction, + = Partial Reduction, ++ = Complete Reduction

[*] The original Kinyoun carbolfuchsin stain was used in conjunction with the Ziehl-Neelsen decolorizer and methylene blue counterstain

3 *Rate of Growth*

The following simple technique was devised as a means of characterizing the various cultures studied in terms of their rate of growth and duration of initial lag phase A 0 1 ml volume from the initial seven day liquid culture of each strain was inoculated into 7 5 ml of Dubos Tween 80 medium in individual Klett tubes which were then incubated at 37° C Utilizing a Klett-Summerson photocolorimeter, Model 800 3, daily readings were made and recorded on each culture

4 *Oxidation-Reduction of Dyes and Neutral Red Test*

After the determination of gross colony morphology, the 21 day cultures on Lowenstein medium were used as the source material for oxidation-reduction dye and neutral red tests The dyes selected for the oxidation-reduction tests were indophenol sodium and 2, 6 dibromoindophenol sodium and the technique utilized was that described by Wilson, et al [18] as modified by Winkle and Patnode [19] The neutral red tests were done according to the procedure described by Dubos and Middlebrook [20] Cultures of M phlei, M butyricum, M smegmatis and M ranae were included in the series of both tests in order to evaluate their specificity [*]

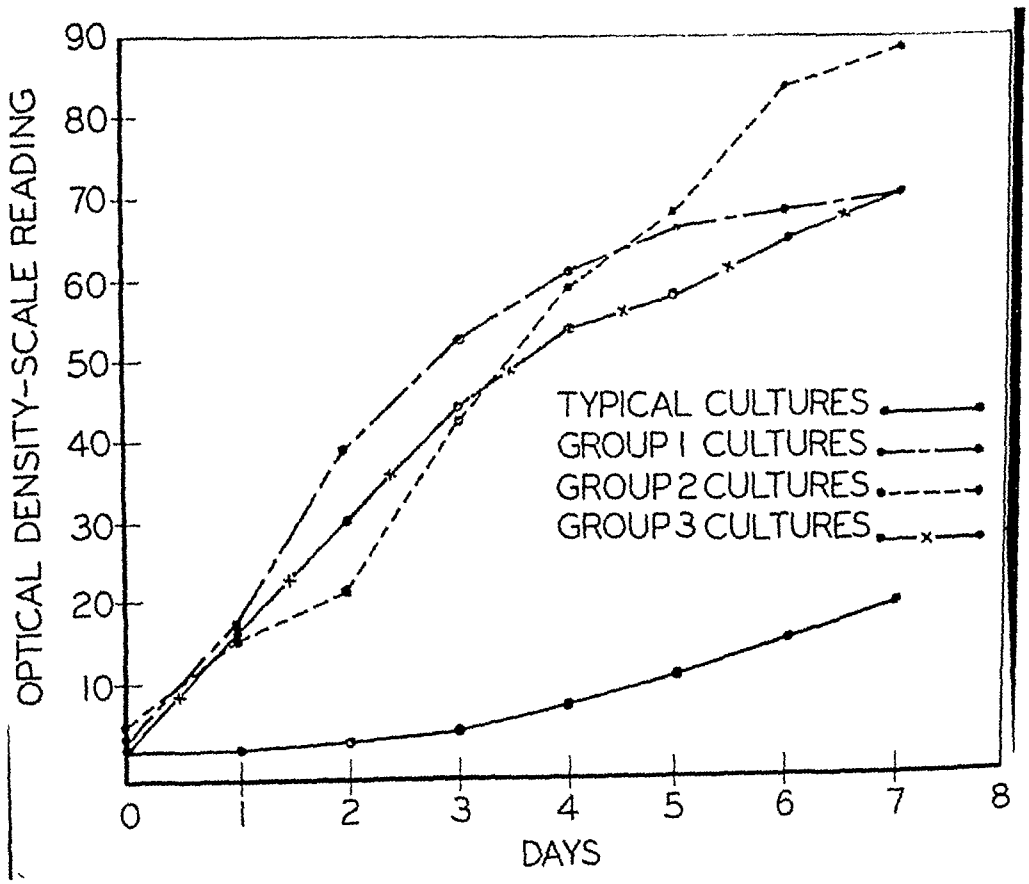


FIGURE 1 Growth of typical and atypical acid-fast cultures in liquid Dubos-Tween 80 medium

[*]Kindly provided for this study by Dr Guy Youmans, Department of Bacteriology, Northwestern University Medical School

5 *Determination of Catalase Activity*

Actively growing cultures on Lowenstein medium were employed for the catalase test according to the procedure outlined by Middlebrook [21] A drop of the peroxide-tween solution at room temperature was deposited upon the culture to be tested The active evolution of gas bubbles within two or three seconds was interpreted as a highly positive (++) catalase reaction If there was marked gas formation within seconds, the test was reported moderately positive (+) The production of slight but definite amounts of gas within a thirty second period was interpreted as a weakly positive (±) catalase reaction

6 *Drug Sensitivity*

The sensitivity or resistance of each culture to the standard anti-tuberculous drugs was determined by the following method A volume of 0 1 ml of the initial seven day liquid culture was placed in quadrants of Felsen plates containing standard Lowenstein medium and varying drug concentrations as follows isoniazid, 0 2, 1 0, and 5 mcg per ml , streptomycin, 3 0, 10 and 100 mcg, per ml , and PAS 0 1, 1 0, and 10 mcg per ml In the preparation of the medium a 50 per cent loss of isoniazid and PAS in the medium was assumed to occur and the concentrations of these drugs were adjusted to compensate for this However, no drug loss was anticipated to occur in the case of streptomycin The results of the drug sensitivity tests were determined after 14 days incubation at 37° C It should be pointed out that the typical cultures were initially selected so that their drug sensitivities would approximate more closely the levels encountered in the atypical strains In order to accomplish this the typical cultures were obtained from patients who had been on long-term chemotherapy and they were not selected from primary isolations

7 *Guinea Pig Virulence*

Subcultures of each strain in Dubos Tween 80 medium were prepared These were observed photelometrically and at the time they were in the

TABLE II

RESULTS OF OXIDATION-REDUCTION DYE TESTS ON TYPICAL, ATYPICAL AND SAPROPHYTIC ACID-FAST CULTURES

	Dibromoindiphenol Sodium			Indophenol		
	Complete Reduction	Partial Reduction	No Reduction	Complete Reduction	Partial Reduction	No Reduction
Typical Cultures	0	1	10	0	1	10
Group I Cultures	8	2	2	7	4	1
Group II Cultures	0	3	0	1	1	1
Group III Cultures	5	5	0	5	4	1
Saprophytic Cultures	4	0	0	4	0	0

maximum growth phase (7-15 days) were transferred to Hopkins vaccine tubes and centrifuged at 3,000 r p m for 30 minutes One cubic mm of sedimented cells was assumed to equal one mg wet weight of tubercle bacilli [22] Two tuberculin negative guinea pigs were inoculated, one subcutaneously and one intraperitoneally, with each strain One cubic mm of sedimented cells, suspended in 0 5 ml of sterile, distilled water was used for each guinea pig inoculation The animals were weighed and tuberculin tested (O T 1 30) weekly The guinea pigs which died were autopsied, gross pathology was noted, direct smears for acid-fast bacilli were made of the organs involved, and cultures were made of the spleens At six weeks the surviving guinea pigs were sacrificed and examined in the same manner as those which had died

8 *Clinical Course and Correlation with Resected Specimens*

The clinical course of each patient included in this study and the role of the atypical bacilli as etiologic agents were carefully evaluated When available, surgical specimens were cultured and the character of the gross and microscopic pathology determined

Results

Since the validity of the initial tentative classification of the atypical cultures into three groups was immediately strengthened and confirmed, the specific results obtained in this study will be discussed within these categories The basic information obtained is summarized in Table I, which also specifies the origin of both the typical and atypical acid-fast cultures included in the series

An evaluation of the appearance and pigmentation of the colonial growth on Lowenstein medium before and after exposure to the light was most meaningful The results obtained were found to be consistent within themselves and to have significance in terms of all of the other factors tested

1 *Colonial Morphology*

a Typical—Growth originating from these cultures developed cream-colored, discrete colonies which showed no change in color as a consequence of 24 hours exposure to light at room temperature

TABLE III

RESULTS OF NEUTRAL RED TESTS ON TYPICAL, ATYPICAL AND SAPROPHYTIC ACID-FAST CULTURES

	Positive	Negative
Typical Cultures	11	0
Group I Cultures	0	12
Group II Cultures	0	3
Group III Cultures	3	7
Saprophytic Cultures	0	4

b Group I—Growth from these cultures also gave rise to cream-colored, discrete colonies of typical appearance which, however, became lemon-yellow after 24 hours exposure to light at room temperature

c Group II—Cultures of these strains gave rise to white, beige, or buff to yellowish confluent growth with little or no tendency to form discrete colonies and there was no acquisition of pigment after light exposure

d Group III—These cultures produced a brilliant orange pigmentation of the colonies which tended to grow luxuriantly and to become confluent The pigmentation appeared during incubation in the dark and was not modified by exposure to the light

2 *Cellular Morphology*

An analysis of the characteristics of the cellular forms seen in Kinyoun stained smears of liquid cultures of the strains included in this study was found to be of value only in differentiating between typical and atypical organisms The differences encountered among the various atypical strains did not seem to be sufficiently uniform among themselves to permit them to be used as distinguishing criteria However, in all instances, the differentiation between typical and atypical strains was possible The following summary details these observations

a Typical—On gross inspection these smears were blue in color, although on microscopic examination the individual bacilli were acid-fast Definite cording was always found and the cells appearing rod-like and measuring 2 to 3 5 micra in length by about 0 5 micra in width

b Group I—On gross inspection these smears were red so that they

TABLE IV
DRUG SUSCEPTIBILITY OF CULTURES OF TYPICAL AND ATYPICAL ACID-FAST BACILLI

	Amount of Growth*	SM mcg/ml 3	10	100	PAS mcg/ml 0 1	1 0	10	INH mcg/ml 0 2	1 0	5 0
	+	3	1	0	0	0	0	1	0	0
Typical	±	7	5	4	9	7	5	5	5	2
Cultures (11)	0	1	5	7	2	4	6	5	6	9
Group I	+	12	7	2	12	8	0	7	1	1
Atypical	±	0	5	7	0	4	12	5	10	10
Cultures (12)	0	0	0	3	0	0	0	0	1	1
Group II	+	2	1	0	3	2	2	3	2	2
Atypical	±	1	2	3	0	1	1	0	1	1
Cultures (3)	0	0	0	0	0	0	0	0	0	0
Group III	+	7	3	0	10	8	2	9	1	1
Atypical	±	3	7	8	0	2	8	1	7	6
Cultures (10)	0	0	0	2	0	0	0	0	2	3

*+ = Growth equal to that of control
± = Growth present but less than that seen in control
0 = No growth

could be readily differentiated from those of typical organisms As would be expected, the individual bacilli were highly acid-fast The individual Group I cultures varied from those showing no cords to some with definite cording In eleven of the cultures the cells varied in length from 1 5 to 3 micra and frequently were noted to contain granules giving rise to a banded appearance However, one of the Group I cultures had cells which were as long as 10 micra and presented a bizarre banded appearance

c Group II—The staining properties of these cultures were identical with those noted in the Group I strains However, the Group II cultures showed a slight tendency to form cords The individual cells measured 2-3 5 micra in length and no granules were seen

d Group III—Smears of these cultures stained intensely red and resembled the other atypical cultures in this respect The cells clumped together showing almost no evidence of cording The individual cells had polar granules which tended to give them a dumbbell shaped appearance They appeared shorter and stubbier than typical bacilli, measuring 1 5 to 2 micra in length by 0 5 micra in width

3 *Rate of Growth in Liquid Medium*

As demonstrated in Figure 1, all categories of atypical bacilli had a very short latent period reaching an arithmetic phase of growth in less than 24 hours The cultures of typical tubercle bacilli had the expected latent period of almost four days before growth was well established At 48 hours it was possible to distinguish clearly between the typical and the atypical strains on the basis of the initial rates of growth as measured turbidimetrically and this is shown in Figure 1

Culture number nine, a Group I atypical, was the only exception to this observation in that it had a very long latent period resembling a typical strain, in this respect However, subsequent subcultures of strain number nine demonstrated rapid growth within 24 hours Repeated subcultures of the typical strains failed to change their basic growth pattern and in no instance was the initial latent period shortened

4 *Oxidation-Reduction of Dyes*

The results of these tests are summarized in Tables I and II The typical cultures failed to reduce the dyes with one exception in which partial reduction was observed The atypical cultures reduced the dyes completely or partially in 45 out of 50 tests (90 per cent) The known saprophytes completely reduced both dyes in all instances Thus, the results of the oxidation-reduction tests, utilizing indophenol sodium and dibromoindophenol sodium respectively, were of value in differentiating the various cultures studied The results obtained appeared to be consistent within the various categories tested in somewhat more than 90 per cent of the strains studied

5 *Neutral Red Test*

The results of these tests are summarized in Tables I and III and it can be seen that they were of considerable value in differentiating the typical from the atypical cultures All of the typical cultures of tubercle bacilli were

found to give a positive reaction to the neutral red test On the other hand, 22 of the 25 atypical cultures demonstrated negative neutral red tests All of the known saprophytes (M phlei, M butyricum, M smegmatis, and M lanae), included for comparison, gave a negative reaction to the neutral red test Thus, these results are in general conformity with those obtained in the oxidation-reduction tests In both the neutral red and oxidation reduction tests, the results obtained suggested that the typical cultures reacted quite uniformly and in fairly clear contradistinction to the response of the atypical strains which more closely followed the reactions manifested by the saprophytic organisms

6 *Catalase Reaction*

The results of the catalase tests are summarized in Table I In general, the typical cultures tended to give less pronounced catalase reactions than

TABLE V

RESPONSE OF GUINEA PIGS INOCULATED WITH 1 0 mg WET WEIGHT OF CULTURES OF TYPICAL AND ATYPICAL ACID-FAST BACILLI

		Animals Dying Before 6 Weeks					Animals Sacrificed at 6 Weeks				
			Mantoux Test					Mantoux Test			
	Route	Number	Positive	Negative	Typical Lesions	Positive Smears	Number	Positive	Negative	Typical Lesions	Positive Smears
Eleven											
Typical	IP (11)	8	5	3	8	8	3	3	0	3	3
Cultures	SQ (11)	6	4	2	6	6	5	5	0	5	5
TOTAL		14	9	5	14	14	8	8	0	8	8
Twelve											
Group I	IP (12)	6	1	5	6	6	6	6	0	6	5
Cultures	SQ (12)	1	0	1	1	1	11	10	1	9	9
TOTAL		7	1	6	7	7	17	16	1	15	14
Three											
Group II	IP (3)	3	3	0	3	3	0	0	0	0	0
Cultures	SQ (3)	3	3	0	3	3	0	0	0	0	0
TOTAL		6	6	0	6	6	0	0	0	0	0
Ten											
Group III	IP (10)	2	0	2	0	0	8	5	3	3	1
Cultures	SQ (10)	2	0	1	2	1	8	6	2	6	2
TOTAL		4	0	3	2	1	16	11	5	9	3

did the atypical strains Thus, 23 out of the 25 atypical cultures demonstrated maximum catalase activity while none of the typical strains did so

7 *Drug Sensitivity*

The data obtained regarding the sensitivity of the typical and atypical strains to the standard antituberculous drugs are summarized in Table IV It can be seen that the typical cultures manifested varying degrees of resistance to the drugs tested and, in this respect, conformed with the patterns of sensitivity normally encountered in our hospital experience with retreatment cases of tuberculosis None of the typical cultures demonstrated complete resistance to streptomycin, isoniazid, or PAS at the highest concentration tested In general, the atypical cultures were more resistant to all of the drugs and no instances of complete sensitivity to any single agent were observed among them Furthermore, no single group of the atypical cultures was found to be directly correlated with resistance to any specific antituberculous drug The atypical cultures of all groups appeared to be more highly resistant to PAS than to the other two drugs tested

8 *Guinea Pig Inoculation*

The results of the virulence studies on guinea pigs are summarized in Table V It can be seen that most of the guinea pigs injected with standardized inocula of typical cultures of tubercle bacilli died within six weeks from the time of inoculation They lost weight and those that survived long enough developed tuberculin sensitivity Lesions grossly characteristic of tuberculosis were seen in all of these guinea pigs at autopsy and smears made of involved tissues were uniformly positive for typical acid-fast bacilli Furthermore, we noted that the cultures comprising our Group II classification gave rise to similar results on guinea pig inoculation with those we obtained from the typical strains Thus, the eleven typical cultures and the three atypical Group II strains demonstrated identical patterns of guinea pig virulence both on intraperitoneal and subcutaneous inoculation These results are quite different from those obtained with the other atypical acid-fast organisms

The Group I atypical cultures did not appear to be as virulent for guinea pigs as were the typical and Group II strains Employing equivalent dosage we found that the six out of the 12 guinea pigs inoculated intraperitoneally with the Group I cultures died within six weeks while 11 out of the 12 animals injected subcutaneously survived the full 42 day period However, at autopsy, lesions grossly characteristic of tuberculosis were seen in 22 out of 24 guinea pigs injected with Group I atypical cultures and smears of the involved tissues were usually positive for acid-fast bacilli It was our opinion that the guinea pigs injected intraperitoneally with Group I strains showed greater involvement of the omentum and serosal tissues than did the animals receiving similar inoculations of typical cultures However, it can be seen that in two instances, the Group I atypical cultures failed to produce obvious progressive disease beyond the site of inoculation in the guinea pigs

On the other hand, the Group III atypical cultures were even less virulent as manifested by their decreased tendency to produce progressive disease in guinea pigs Sixteen out of 20 of the animals with Group III strains survived six weeks and, at autopsy, none showed more than minimal involvement of the spleen The guinea pigs which were inoculated subcutaneously, in addition, had local abscesses visible at the site of injection In no instance was a guinea pig inoculated with a Group III culture found to have widely disseminated disease However, of the 16 animals surviving six weeks after inoculation with Group III cultures, 11 were found to be tuberculin positive

The guinea pig tests seemed to be conclusive in demonstrating a gradation in virulence among the acid-fast organisms tested The typical cultures and Group II strains appeared to be equally virulent for guinea pigs However, the Group I atypical cultures seemed to be somewhat less virulent, while the Group III strains appeared to be least capable of producing progressive or fatal disease

9 *Clinical Course*

Careful analysis of the records of the patients from which the typical and atypical cultures were obtained suggested certain general correlations which appeared to be consistent (Tables I and VI) The 11 patients who were the sources of the typical cultures, never produced Group I or II organisms in many cultures taken of sputum, pharyngeal secretions, or gastric contents However, two of these patients did produce Group III cultures late in the course of their disease In addition, these 11 patients all had the classical pulmonary lesions of tuberculosis From eight of these patients surgical specimens were obtained, all of which were positive on culture for typical human type tubercle bacilli The disease encountered in these patients ranged from minimal to far advanced and no other disease process was either suspected or detected

The 12 patients from whom the Group I atypical cultures were obtained all manifested disease which was clinically indistinguishable from classical pulmonary tuberculosis and ranged in character from minimal to far advanced It has been our impression that the far advanced cases with Group I infections responded less well and more slowly to chemotherapy than did

TABLE VI

X-RAY CLASSIFICATION OF PULMONARY DISEASE ENCOUNTERED IN PATIENTS

	Typical	Group I	Group II	Group III
Minimal	3	3		2
Moderately Advanced		3	1	2
Far Advanced	8	6	2	5
Questionable				1
TOTAL	11	12	3	10

comparable patients from whom typical tubercle bacilli were recovered However, this difference to some extent may be accounted for by the trend toward higher drug resistance demonstrated by the Group I cultures Seven of the patients with Group I infections were operated upon and the pathological specimens all demonstrated the typical histological findings diagnostic of tuberculosis except for one patient whose pulmonary tissues demonstrated only non-specific chronic inflammation However, this patient was highly sensitive to tuberculin (O T 1 10,000) All of the surgical specimens were positive on culture for Group I atypical organisms It should be pointed out that the 12 patients from whom the Group I photochromogens were isolated never produced typical virulent tubercle bacilli on culture

Group II cultures, characterized by rapid confluent growth, were obtained from only three patients and no surgical or autopsy specimens were available for study These three patients were always consistent in their production of Group II cultures and at no time were their cultures positive for typical tubercle bacilli or acid-fast chromogens Clinically, the disease seen in two of the patients was classified as far advanced and in the third case it was moderately advanced (Tables I and VI) The disease seen in these patients was indistinguishable from pulmonary tuberculosis caused by typical organisms It was our impression that, although all three of these patients improved on conventional chemotherapy regimens, their general response was much slower and less striking than would have been anticipated in comparable cases infected with typical organisms

The 10 strains of Group III atypical organisms were all characterized by their ability to form an orange pigment independent of light stimulus in the colonies grown on solid media These organisms were obtained from either sputum, pharyngeal, or gastric cultures An analysis of the clinical records of the 10 patients from whom the Group III organisms were isolated confirmed our impression that these particular atypical strains as a rule were isolated only from patients who had prolonged clinical courses and, in all but two instances, been on long-term chemotherapy In no instance was a Group III strain isolated from a patient with only fresh disease In the great majority of cases, these organisms were recovered from patients who originally had only typical tubercle bacilli in their cultures and then had become culture negative for a period of time after which the Group III isolation would occur In our experience, Group III cultures never have initiated progressive, active pulmonary tuberculosis Three of the patients from whom Group III cultures were obtained had pulmonary resections in the course of their hospitalization and in each instance the typical lesions of tuberculosis were found in the surgical specimens

Discussion

The benefits derived from the increasing use of effective cultural techniques for the isolation of tubercle bacilli have been great, both in terms of greater diagnostic accuracy and also in the proper evaluation of therapy However, the more frequent use of *such techniques has also created a*

practical problem related to the apparent increased frequency with which atypical acid-fast organisms are being isolated from patients In many cases it is difficult to evaluate the significance of these atypical mycobacteria and, too frequently, there has been the temptation to regard them as non-pathogenic [3 4 6 11, 23]

During the past several years we have noted that approximately one-fourth of our patients had cultures reported positive for atypical acid-fast bacilli at one time or another in their clinical course Careful observation of these atypical cultures promptly led us to certain impressions concerning their significance and relationship to the pulmonary disease found in the patients from whom they were isolated Therefore, it seemed important to set up a study in which the biological characteristics of representative strains of these atypical organisms were compared with those of cultures of typical, human type tubercle bacilli isolated under similar conditions

Cursory inspection of the atypical acid-fast cultures obtained from our patients indicated that they were readily separated into three groups on the basis of their growth on solid media The strains which gave rise to typical colonies which became pigmented on exposure to the light (photochromogenic) were included in Group I The strains which formed confluent, diffuse growth on solid media and did not become pigmented on exposure to light were included in Group II Finally, the Group III strains consisted of cultures which grew luxuriantly on solid media and produced an orange pigmentation in the dark (skotochromogenic)

In general, the atypical strains studied revealed sharp differences in their behavior in terms of cellular and colonial morphology, biochemical reactions, and pathogenicity for guinea pigs as compared to the typical cultures However, as would be expected, the individual variations were great and, in terms of any specific test, there was considerable overlapping so that it was not possible to separate completely the typical from atypical cultures on the basis of any single reaction Actually, the original classification based upon colonial morphology appeared to be as valid as that derived on any other basis These results are not surprising when one considers the wide range of variations which have been recognized in the morphology, biochemical reactions, and virulence of human type tubercle bacilli [24 25]

In our experience, Group I atypical acid-fast cultures have always been isolated from patients with disease which is clinically and pathologically identical with tuberculosis In these patients it has been the only organism recovered from their sputum and in untreated cases it always has been associated with progressive, invasive disease Although these strains, in general, have shown increased resistance to the standard antituberculous drugs, not all cultures are highly resistant to any single chemotherapeutic agent Thus, it seems unlikely that these strains can be related to the acquisition of resistance to either streptomycin, PAS, or isoniazid

Cultures classified by us as Group II atypical acid-fast strains are quite rare in our experience However, when present, they are associated with progressive disease clinically indistinguishable from classical tuberculosis

The patients from whom Group II cultures have been obtained never produce any other type of acid-fast bacilli nor do we believe that the presence of such atypical organisms can be correlated with resistance to any single antituberculous drug

On the other hand, our experience suggests that the Group III atypical organisms are much less clearly related to the presence of active, invasive pulmonary tuberculosis than are either Group I or Group II strains At no time have we isolated a Group III culture from a patient who did not have evidence of old, relatively stable and quiescent disease of long clinical duration and who had, in the majority of instances, received a long course of chemotherapy As a rule, the patients from whom Group III organisms were obtained had previous isolations of typical or, in a few cases, Group I strains from cultures taken earlier in the course of their disease At the present time, however, we feel that the cultures classified by us as Group III are much less homogenous in all respects than are the other types of atypical organisms reported In general, it is our impression that the majority of Group III isolations occur in patients shortly before they become definitely culture negative It is noteworthy that our efforts to recover such organisms from individuals known to be free from pulmonary tuberculosis have always failed

At the present time we can offer no logical explanation to account for our experience with the Group III organisms We cannot escape the conclusion that the isolation of such an organism bears a significant relationship to previously active pulmonary tuberculosis but we can find no suggestion in our patients or their contacts to support the classification of the Group III acid-fast bacilli as highly pathogenic mycobacteria The absence of significant resistance to any single antituberculous drug on the part of the Group III cultures makes it difficult for us to believe they can be accounted for on the basis of their being drug-resistant mutants or variants However, at present this possibility cannot be eliminated entirely

Our experience has convinced us that the isolation of Group I or Group II cultures from a patient must be considered meaningful and should be regarded as a definite indication for the initiation of antituberculous chemotherapy This recommendation is made in spite of the fact that our experimental results clearly reveal that Group I and Group II cultures show growth and biochemical characteristics approaching or identical to those of known acid-fast saprophytes However, the results of guinea pig inoculation certainly suggest that cultures of these two groups are virulent This view, of course, is even more strongly supported by the characteristics of the disease encountered in the patients from whom these cultures were isolated Therefore, we believe that the confirmed isolation of either Group I or II cultures is an immediate and proper justification for chemotherapy and for a diagnosis of tuberculosis In terms of our present knowledge we feel that it would be unfair and imprudent to withhold a diagnosis of tuberculosis from those patients consistently yielding such atypical organisms on culture in association with clinical evidence of disease

The Group III cultures that we have encountered appear to have definite

significance in terms of the biological history of tuberculosis in the individuals from whom they are isolated In general, we feel that the presence of such atypical cultures is a good prognostic omen, however, inasmuch as the majority of these patients were culture-positive for typical organisms in their immediate past, we feel that full and adequate chemotherapy should be continued in these patients until the traditional criteria for cessation of treatment are fulfilled plus complete absence on repeated culture of the Group III bacilli

We have observed a few individuals who were positive for Group III cultures on the occasion of their initial diagnostic workup It is our opinion that these patients should receive full courses of chemotherapy if they have any pulmonary pathology detectable If no evidence of clinical disease can be found, such patients must be most carefully observed and re-evaluated at frequent intervals

SUMMARY

The characteristics of 25 atypical and 11 typical cultures, obtained from 36 patients with pulmonary tuberculosis, were studied in terms of 1) Colonial and cellular morphology, 2) Rate of growth in liquid medium, 3) Drug sensitivity, 4) Oxidation-reduction of dyes, catalase reaction, and neutral red tests, 5) Guinea pig virulence, and 6) The characteristics of the clinical disease encountered in these cases

We were able to classify the atypical organisms as follows Group I, consisting of 12 cultures which produced typical colonies and developed lemon-yellow pigmentation on exposure to light (photochromogenic), Group II, comprising three cultures which produced confluent growth with little tendency to form discrete colonies and showed no pigmentation, and Group III, consisting of 10 cultures which produced yellow-orange colonies in the dark (skotochromogenic) In general, the atypical organisms showed a rapid rate of initial growth in liquid Dubos medium, complete or partial reduction of the oxidation-reduction dyes, highly positive catalase reactions, and negative neutral red tests Guinea pig inoculation revealed that Group I and II strains were virulent The Group III organisms, however, were uniformly much less virulent The atypical cultures were not markedly different from the typical strains in their sensitivity to streptomycin, PAS and isoniazid

Review of the clinical records of the 25 patients from whom the atypical cultures were isolated, suggested certain correlations The 15 infected with Group I and II strains all had significant pulmonary disease, clinically indistinguishable from tuberculosis caused by typical organisms, and at no time in their clinical course were cultures of typical organisms obtained These 15 patients responded more slowly to chemotherapy than did those infected with typical strains The 10 Group III strains all were isolated from patients with long-standing pulmonary tuberculosis who had responded satisfactorily to chemotherapy and from whom typical organisms had been recovered in sputum cultures obtained during the earlier phases of their disease The Group III strains did not cause progressive

disease in any patient Furthermore, recovery of Group III strains was rarely followed at a later time by the isolation of typical cultures from the same patient

RESUMEN

Se estudiaron las características de 25 cultivos atípicos y 11 típicos obtenidos de enfermos de tuberculosis pulmonar en relación con 1) Morfología celular y de las colonias, 2) Proporción de crecimiento en medio líquido, 3) Sensibilidad a las drogas, 4) Oxidación-reducción de colorantes, reacción de la catalasa y del rojo neutro, 5) Virulencia para el cuy y 6) Las características de la enfermedad clínica en estos casos

Podemos clasificar los organismos atípicos como sigue Grupo I, consistente en 12 cultivos que produjeron colonias atípicas y presentaron pigmentación amarillo limón al exponerse a la luz (fotocromogenicos) Grupo II, que comprende tres cultivos que produjeron crecimiento confluente con poca tendencia a hacer colonias discretas y no mostraron pigmentación, y Grupo III, de diez cultivos que produjeron colonias pigmentadas amarillo naranja en la obscuridad (escotocromogénicos) En general los organismos atípicos mostraron un rapido crecimiento inicial en medio líquido de Dubos, reducción completa o parcial de los colorantes de la oxidación-reducción, reacciones altamente positivas de la catalasa, y reacciones negativas del rojo neutro La inoculación al cuy reveló que los grupos I y II eran virulentos Sin embargo el grupo III fueron uniformemente menos virulentos Los cultivos atípicos no fueron notablemente diferentes de los típicos en cuanto a su sensibilidad a la estreptomicina, PAS e isoniacida

La revisión de los expedientes clínicos de 25 enfermos de quienes se aislaron cultivos atípicos, sugirieron ciertas correlaciones

Los 15 infectados con el grupo I y II tenían todos enfermedad pulmonar franca, que no se podía distinguir de la tuberculosis causada por la cepas típicas, y en ningún tiempo de su evolución clínica se obtuvieron cultivos típicos de ellos Estos 15 enfermos respondieron más lentamente a la quimioterapia que los infectados con cepas típicas

Los 10 del grupo III fueron aislados de enfermos con tuberculosis de larga duración que habían respondido satisfactoriamente a la quimioterapia y de quienes se habían obtenido organismos típicos en fases anteriores de su enfermedad

El grupo III no causo enfermedad progresiva en ningún enfermo

Más aún, el hallazgo de cepas III rara vez fué seguido más tarde de aislamiento de cepas típicas en el mismo enfermo

RESUME

Les caractéristiques de 25 cultures atypiques et II cultures typiques, obtenues d'après 36 malades atteints de tuberculose pulmonaire, ont été étudiées sur les bases suivantes

1) morphologie cellulaire et morphologie de la colonie,

2) taux de croissance en milieu liquide,

3) sensibilité à la médication,

4) oxydation-réduction des colorants, réaction à la catalase, et tests au rouge neutre,

5) virulence sur le cobaye,

6) caractéristiques de la maladie clinique rencontrée dans ces cas

L'auteur put classer les germes atypiques comme il suit Groupe I, qui comporte 12 cultures qui produisirent des colonies typiques et donnèrent lieu à une pigmentation jaune-citron a l'exposition à la lumière (photochromogéniques), Groupe II, qui comprend trois cultures qui montrèrent une croissance confluente, avec une petite tendance à la formation de colonies discrètes et qui ne produisirent aucune pigmentation, Groupe III, consistant en 10 cultures, qui formerent des colonies jaune orange à l'ombre (skotochromogéniques) En général, les microbes atypiques montrèrent un taux rapide de croissance initiale en milieu liquide de Dubos, une réduction complète ou partielle de l'oxydation-réduction des colorants, des réactions à la catalase hautement positives, et des tests au rouge neutre négatifs L'inoculation au cobaye révéla que les souches des groupes I et II étaient virulentes Les microbes du groupe III cependant, furent uniformément moins virulents Les cultures atypiques ne purent pas nettement se différencier des souches typiques par leur sensibilité à la streptomycine, à l'acide para-aminosalicylique, et à l'isoniazide

La revue des rapports cliniques concernant les 25 malades chez qui les cultures atypiques furent isolées, évoque certaines corrélations Les 15 malades infectés avec des souches des groupes I et II avaient une atteinte pulmonaire importante, cliniquement indiscernable de la tuberculose causée par des germes typiques, et à aucun moment de leur évolution clinique on ne put obtenir des cultures de germes typiques Ces 15 malades répondirent plus lentement à la chimiothérapie que ceux infectés par des souches typiques Les 10 souches du groupe III furent toutes isolées chez des malades atteints de tuberculose pulmonaire datant de longtemps, qui avaient répondu favorablement à la chimiothérapie, et chez qui les bacilles typiques avaient été recueillis dans les cultures d'expectoration obtenues pendant les phases précoces de leur affection Les souches du Groupe III ne furent cause d'aucune atteinte extensive chez les malades En outre, après avoir recueilli des souches du groupe III, rarement chez le même malade furent isolées ensuite des cultures typiques

ZUSAMMENFASSUNG

Die Charakteristika bei 25 atypischen und 11 typischen Kulturen, die von 36 Patienten mit Lungentuberkulose gewonnen wurden, wurden untersucht unter Berucksichtigung von 1) Morphologie von Kolonien und Zellen, 2) Wachstumsrate in flussigen Nahrboden, 3) Arzneimittel-Empfindlichkeit, 4) Reduktion von Farbstoffen durch Oxydation, Katalase Reaktion und Neutralrotproben, 5) Meerschweinchen-Virulenz, und 6) die Charakteristika der bei diesen Fallen vorliegenden klinischen Erkrankung

Wir vermochten die atypischen Organismen wie folgt zu klassifizieren Gruppe I, bestehend aus 12 Kulturen, die typische Kolonien bildeten und eine zitronengelbe Pigmentierung hervorbrachten nach Licht-Exposition (photochromogen), Gruppe II umfasst 3 Kulturen, die ein konfluierendes Wachstum bewirkten mit geringer Tendenz zur Bildung diskreter Kolonien, und die keine Pigmentierung zeigten, und Gruppe III, bestehend aus 10 Kulturen, die im Dunkeln orangegelbe Kolonien bildeten (skotochromogen) Im allgemeinen zeigten die atypischen Organismen eine schnelle anfangliche Wachstumsrate in Dubos' flussigem Nahrboden, eine komplette oder partielle Reduzierung der durch Oxydation reduzierenden Farbstoffe, stark positive Katalase-Reaktionen und negative Neutralrotproben Meerschweinchen-Impfungen ergaben, dass die Stamme der Gruppe I und II virulent waren Einheitlich waren die Organismen der Gruppe III jedoch erheblich weniger virulent Die atypischen Kulturen differierten nicht entscheidend gegenuber typischen Formen in ihrer Sensibilitat auf Streptomycin, PAS und INH

Eine Durchsicht der klinischen Aufzeichnungen der 25 Kranken, von denen die atypischen Kulturen gewonnen wurden, lassen gewisse Beziehungen vermuten Die 15 Tragen von Stammen der Gruppe I und II hatten samtlich eine beträchtliche Lungenerkrankung, die klinisch nicht zu unterscheiden war von einer durch typische Organismen verursachten Tuberkulose, und zu keiner Zeit ihres klinischen Verlaufs ergaben sich Kulturen mit typischen Organismen Diese 15 Patienten reagierten langsamer auf die Chemotherapie als die mit typischen Stammen infizierten Falle Die 10 Stamme der Gruppe III wurden samtlich gewonnen von Patienten mit lang bestehender Lungentuberkulose, die befriedigend auf die Chemotherapie reagiert hatten und bei denen typische Organismen in Sputumkulturen gefunden worden waren, die man wahrend fruherer Phasen ihrer Krankheit angelegt hatte Die Stamme der Gruppe III verursachten bei keinem Kranken eine fortschreitende Erkrankung Darüber hinaus folgte dem Nachweis von Stamme der Gruppe III selten zu einem spateren Zeitpunkt die Isolierung von typischen Kulturen desselben Patienten

REFERENCES

1 Pinner, M "Atypical Acid-Fast Micro-organisms III Chromogenic Acid-Fast Bacilli from Human Beings," *Am Rev Tuberc*, 32 424, 1935

2 Tarshis, M S and Frisch, A W "Chromogenic Acid-Fast Bacilli from Human Sources I Cultural Studies," *Am Rev Tuberc*, 65 278, 1952

3 Lagercrantz, R, Olhagen, B and Wickman, K "Acid-Fast Rods in Sputum Simulating Tubercle Bacilli," *Acta Med Scandinav*, 147 50, 1953

4 Yegian, D and Budd, V "Certain Nonpathogenic Mycobacteria As a Source of Error in Diagnosis and Drug Susceptibility Tests," *Am Rev Tuberc*, 68 557, 1953

5 Timpe, A and Runyon, E H "The Relationship of 'Atypical' Acid-Fast Bacteria to Human Disease," *J Lab and Clin Med*, 44 202 1954

6 Ribbins, E S, Baum, G L and Schwarz, J "Chromogenic Acid-Fast Bacilli," *J Lab and Clin Med*, 45 546, 1955

7 Pollak, A and Buhler, V B "The Cultural Characteristics and Animal Pathogenicity of an Atypical Acid-Fast Organism Which Causes Human Disease," *Am Rev Tuberc*, 71 74, 1955

8 Wilson, G C and Morton, D E "The Clinical Incidence of Acid-Fast Bacilli Nonpathogenic for Guinea Pigs," *Am Rev Tuberc*, 73 351, 1956

9 Wood, L E, Buhler, V B and Pollak, A "Human Infection With the 'Yellow' Acid-Fast Bacillus," *Am Rev Tuberc*, 73 917, 1956

10 Florence, H "Atypical Acid-Fast (Chromogenic) Organisms Complicating Pulmonary Disease," *Dis Chest*, 30 250, 1956

11 Symposium on Saprophytic Acid-Fast Bacilli in Lesions Simulating Tuberculosis, *Proc Staff Meet, Mayo Clin*, 31 238, 1956 (a) Weed, L A Introduction, 238, (b) Weed, L A, Karlson, A G, Ivins, J C and Miller, R H Recurring Migratory Chronic Osteomyelitis Associated with Saprophytic Acid-Fast Bacilli Report of a Case of 10 Years' Duration Apparently Cured by Surgery, 238 (c) Weed, L A, McDonald, J R and Needham, G M The Isolation of "Saprophytic" Acid-Fast Bacilli from Lesions of Caseous Granulomas, 246 (d) Weed, L A, Keith, H M and Needham, G M Nontuberculous Acid-Fast Cervical Adenitis in Children, 259

12 Runyon, E H "Veterans Administration, National Tuberculosis Association Cooperative Study of Mycobacteria," *Am. Rev Tuberc*, 72 866, 1955

13 Diagnostic Procedures and Reagents, Ed 3 *American Public Health Association*, New York, 250, 1950

14 Tarshis, M and Frisch, A W "Blood Media in the Cultivation of Mycobacterium Tuberculosis," *Am J Clin Path*, 21 101, 1951

15 Dubos, R J and Middlebrook, G "Media for Tubercle Bacilli," *Am Rev Tuberc*, 56 334, 1947

16 Dubos, R J and Davis, B D "Factors Affecting the Growth of Tubercle Bacilli in Liquid Media," *J Exper Med*, 83 409, 1946

17 Kinyoun, J J "A Note on Uhlenhuth's Method for Sputum Examination for Tubercle Bacilli," *Am Jour Pub Health*, 5 867, 1915

18 Wilson, F J, Kalish, C and Fish, C H "Use of Oxidation-Reduction Dyes in the Determination of Virulence of Mycobacteria in Vitro," *Am Rev Tuberc*, 65 187, 1952

19 Winkle, C K and Patnode, R A "A Test Tube Modification of the Oxidation-Reduction Dye Test for the Determination of Virulence of Mycobacteria in Vitro," *Am Rev Tuberc*, 66 99, 1952

20 Dubos, R J and Middlebrook, G "Cytochemical Reaction of Virulent Tubercle Bacilli," *Am Rev Tuberc*, 58 698, 1948

21 Middlebrook, G "Isoniazid Resistance and Catalase Activity of Tubercle Bacilli A Preliminary Report," *Am Rev Tuberc*, 69 471, 1954

22 Willis, H S and Cummings, M M *Diagnostic and Experimental Methods in Tuberculosis*, Ed 2 Charles C Thomas, 258, 1952

23 Walsh, J J, Linn, R H and Biancato, F "Tuberculous Axillary Adenitis Following Application of P P D," *Ann Int Med*, 45 547, 1956

24 Topley, W W C and Wilson, G S *The Principles of Bacteriology and Immunity*, Ed 2 The Williams & Wilkins Company, 288, 294, 1936

25 Breed, R S, Murray, E G D and Hitchens, A P *Bergey's Manual of Determinative Bacteriology*, Ed 6 The Williams & Wilkins Company, 876-879, 1948

Considerations in Humidification by Nebulization*

IVAN E CUSHING, M D** and WILLIAM F MILLER, M D, F C C P†
Dallas, Texas

Nebulization may provide therapy by medication, humidification, or even by cooling The use of nebulization for humidification has been widely proposed and accepted, but indications and requirements have not been established except by clinical impression, and knowledge of humidity is scant The functions of medication as distinct from humidification have been confused

The purpose of this paper is threefold

1 To show the rational indications and requirements for humidification that can be derived from a consideration of both the available data and the physical processes involved in respiratory tract air conditioning

2 To present data on the production of vapor and liquid humidity by nebulizers operated under various circumstances and to show the effect of temperature and other variables

3 To describe a method of nebulization which provides adequate humidity for continuous intermittent positive inspiratory pressure breathing

Humidity Terminology

In consideration of these matters, it is helpful to use an absolute humidity term having direct physiological meaning Humidities are expressed in two principal ways Relative humidity or per cent saturation at a given temperature expresses "dryness" *at that temperature,* while absolute humidity expressed on a dry air basis permits direct comparison of water content at different conditions *Both* are required to fully express a given humidity

The commonly used absolute humidity expressions such as "grams of water per cubic meter of dry air" or "grains of moisture per pound of dry air" are cumbersome and lack direct physiologic meaning Walley[1] and Marshall[2] have used the term "per cent saturation at body temperature" to relate absolute humidities produced by their devices to the absolute humidity achieved in the body Cole[3] used the expression "per cent water content of lung air" The shorter term "per cent body humidity"

---

*From the Cardiopulmonary Laboratory, Department of Internal Medicine, University of Texas Southwestern Medical School, and Parkland Memorial Hospital
**Research Fellow, University of Texas Southwestern Medical School, under the auspices of the American Trudeau Society and the Dallas Heart Association
†Assistant Professor of Medicine, University of Texas Southwestern Medical School
This study was supported in part by funds from the Dallas Heart Association
Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

(per cent B H) is proposed for this use and utilized in this paper Body humidity is defined as the absolute humidity (water content) of saturated air at body temperature (37° C, 98 6° F, pH_2O of 47 mm of Hg) Per cent body humidity is easily calculated from standard absolute humidity data, or by the equation

$$\text{Per Cent B H} = \frac{pH_2O}{760\text{-}pH_2O} \times \frac{713}{47} \times 100$$

For clinical purposes a simple ratio of $pH_2O/47$ gives values which are within 1 5 per cent B H of the true absolute humidity

The Need for Humidification

A number of investigators have studied air conditioning in the respiratory tract (Ingelstedt's recent paper[4] is a convenient source of reference to the available data) The striking finding in all this work is that inspired air is so easily humidified in normal airways even under adverse circumstances None of the data show significantly dry air reaching the trachea during nasal or even maximal oral respiration, although some observations suggest that warm air should be at above 70 per cent relative humidity to prevent incipient drying or alteration of mucosa near the inlet to the airways[5 6] In addition to the conditioning achieved in the upper airways, warming and humidification are easily completed by the larger surface available in the tracheo-bronchial tree According to calculations from Rohrer's data,[7] the surface area of bronchi down to 1 5 mm diameter amounts to about 700 sq cm as compared to about 220 sq cm in the nose and pharynx and 100 sq cm in the larynx and trachea Thus, it would not be reasonable to assume that small bronchial "inspissated" mucus casts are caused by lack of humidity However, it is well known from clinical experience that serious drying can occur

Since none of the studies on air conditioning have included the disease states in which such drying is most likely, the indications for therapeutic humidification thus far must rest on inference and isolated observations From the studies of normals, it is fairly obvious that some combination of excessively drying air and abnormal humidifying mechanism must be present for airway drying to occur The drying tendency of air depends on its humidity, temperature, volume respired, and rate of flow past the mucosa The humidifying ability of mucosa depends more on the mere presence of a film of moisture at the surface than on any other factor such as surface temperature or concentration of solute in the surface moisture When normal secretions are present, the water vapor pressure driving the humidification process is essentially that of pure water at the surface temperature If such free moisture is absent, vapor pressure at the dry surface is much lower For instance, if a patient breathing through the mouth does not keep saliva spread over the surface, much drier air may reach the trachea than the data on oral respiration in normals would indicate Factors such as dehydration, atropine-like drugs, and reflexes which affect secretory rate can contribute to lower airway drying if they result in grossly dry upper airway surfaces

The most serious drying effects occur in the trachea Since even grossly abnormal upper airways provide some humidification, drying usually occurs in the presence of thick tracheal exudate or with a tracheostomy If thick exudate coats the mucosal surface, a barrier exists between the surface of the exudate and the moisture provided by mucosal secretion, and the surface becomes dry more easily A dry surface in the trachea has a more serious effect than in the nose since all the tracheo-bronchial exudate and secretions must pass upward through the driest area, where the collection of exudate or secretion causes the drying process to be self-perpetuating and progressive Precisely the expected thick, pasty exudate lining the trachea has been observed in comatose patients who have been hyperventilating through a dry mouth, following aspiration

With tracheostomy, breathing room air often causes subjective discomfort, plugging of the tracheostomy tube, and drying and encrustation of exudate or secretions, even with an initially normal tracheo-bronchial tree In the presence of thick exudate, drying can be disastrous However, patients with permanent tracheostomy have surprisingly moderate difficulty in the absence of bronchopulmonary disease

The humidity necessary to prevent ill effects of drying varies considerably To prevent subjective symptoms caused by incipient drying in normal nasal passages, 70 per cent or more relative humidity at 20-27° C (say 25-45 per cent B H) should be sufficient, and less humidity is required at lower temperatures [5] Air at 25° C and near 100 per cent relative humidity (49 per cent B H) further minimizes drying tendency at the inlet and is easily warmed and humidified to conditions which ordinary air reaches only at the hypopharynx or trachea [3] The vapor pressure gradient between mucosal surface and air, which is at least about 20 mm Hg for air at 20° C and 35 per cent relative humidity, is reduced to about half this value by saturated air at 25° C, and once such air has been warmed to about 34° and, say, 98 per cent relative humidity, the mucosal-air gradient is only a few mm of Hg Thus, saturated air at 25° C represents an approximate upper limit to the usefulness of humidity for nasal respiration, even when tracheal exudate is present Slightly higher values might be desirable for oral breathing when tracheal exudate is present

For tracheostomy breathing, the necessary humidity may range all the way from the same minimum conditions necessary to prevent discomfort or alteration of mucosa in the nose,[6] to the normal tracheal inlet conditions of near body temperature, and near 100 per cent saturation (near 100 per cent body humidity) High relative humidity seems more important than high temperature to prevent drying, since even at the same absolute humidity warmer air will result in a slightly higher mucosal temperature and thus increase the mucosa air pH_2O gradient

When drying of tracheal exudate has already occurred, provision of maximum possible humidity is important, and the delivery of liquid water by mist therapy or instillation is helpful in rapidly remoistening the dry exudate Delivery of maximum humidity implies that the air be saturated (or supersaturated) at near body temperature

When tracheal exudate or secretions are a problem, medication has an important role in the therapy of drying The administration of hygroscopic, wetting, and enzymatic agents can be expected to aid in the thinning and elimination of thick exudate and thus help restore normal mucosal humidifying efficiency (Such agents are certainly indicated for therapy of inspissated material in the small bronchi where humidity is already at a maximum and cannot be increased by humidification of inspired air)

The role of pure water mist in the therapy of tracheo-bronchial exudate when humidity is already near maximum is obscure The addition of liquid water has no humidifying effect on a mucosa-exudate-air system which is all at near body temperature and 100 per cent relative humidity Any action by liquid water must be a mechanical one, such as providing a vehicle for the liberation and evacuation of exudate In the same way, droplets containing medication have no humidifying effect when the air is saturated at near body temperature, and when the air is not saturated the mere deposition of the droplets from the gas stream to the mucosa does not change the humidity The therapeutic effect is mechanical or due to the medication

The rational indications for therapeutic humidification of air which has an excessive tendency to produce drying seem to be one or more of the following

1 The presence of subjective discomfort or the possibility of ill effect from incipient drying in the upper airways,

2 The presence of gross drying in the upper airways,

3 The admission of air directly to the trachea as in tracheostomy, and,

4 The presence of excessive, thick tracheobronchial exudate or the inability to move exudate and secretions rapidly through the trachea

The amount of humidity required for therapy may vary from about 70 per cent relative humidity for warm air (less for cooler air) to saturation at near body temperature Mist therapy providing "super saturation" *at near or above body temperature* has a definite role in the therapy of dried exudate, but in the presence of a moist surface and saturated air its therapeutic effect must be due to mechanical factors

Medication has an important therapeutic role when exudate or secretions are a problem, but again, this should not be confused with humidification

Nebulizer Humidity Production

Gas in the contacting chamber of a nebulizer, whether from the jet or that drawn in by aspiration, is saturated with water vapor almost instantly This production of *vapor humidity* depends on temperature and is the same for all devices producing saturation at that temperature (neglecting changes in vapor pressure caused by solutes) This operating temperature of a nebulizer is always lower than the temperature of the surroundings, depending on the amount of evaporation and the surface area of the nebulizer

In contrast, the amount of liquid humidity produced may vary considerably, depending more on particle size than number of particles The range of particle size for high humidity is different from that for effective medication since large particles may evaporate from the surface of the apparatus or moisten upper airway mucosa, thus providing effective humidity but representing ineffective medication to the smaller bronchioles

Alteration of nebulizer mist occurs because of warming in apparatus and in the patient's upper airways These effects are different for humidity and medication When pure water mist is warmed, the finer droplets evaporate rapidly, exchanging liquid for vapor humidity When water vapor is added to the mist simultaneously with warming, as in the airways, pure water droplets may or may not evaporate When airway mucosa is moist so that humidification efficiency is high in comparison to warming efficiency, the droplets should tend to persist When the mist is warmed by radiation or dry mucosa decreases humidification efficiency, more evaporation of the droplets should occur When solute is present, the droplets are "stabilized"[8] and do not completely evaporate on warming of the mist Thus more droplets persist to be deposited in the tracheobronchial tree As discussed in the previous section, a distinction should be made between humidification and the medicinal or mechanical effect of droplets deposited in the tracheobronchial tree

The presence of solute in the nebulizer changes the production of vapor humidity by lowering the vapor pressure Conversely, the production of humidity affects the rate at which medication is delivered The vapor pressure lowering can be estimated by assuming that the ideal solution equations apply, in which case vapor pressure lowering is proportional to mol fraction of solute present A commonly used nebulizer solution* contains 0 44 mol per cent $NaHCO_3$ and 1 1 mol per cent glycerine A 10 per cent propylene glycol solution is 2 6 mol per cent Thus initial vapor humidity lowering in such solutions amounts to about 0 02 times the humidity of pure water at the operating temperature Concentration of the solute as the solution is nebulized increases at a rate which depends on the ratio of solute-free vapor to solute containing liquid produced Nebulizers which may produce 1/3 of their humidity as vapor and 2/3 as liquid will concentrate to about 125-130 per cent of the initial concentration each time one half of the solution is nebulized That is, concentration will rise from 2 per cent initially to about 2 5 per cent, 3 2 per cent, 4 1 per cent, etc , as 1/2, 3/4, 7/8, etc , of the solution is nebulized, respectively The effect is not important in this case However, if a nebulizer with a small liquid humidity production is heated to produce high vapor humidity, vapor humidity will amount to a large fraction of the total humidity In such a case, the rise in concentration approaches that for no loss of solute from the solution That is, 2 per cent initial will rise to about 4 per cent, 8 per cent, 16 per cent, etc , as 1/2, 3/4, 7/8, etc , of the solution is nebulized At such higher concentrations many other factors may be

*Alevaire ®

operable In any event, the vapor humidity and amount of medication produced will change markedly toward the end of nebulization of a given amount of solution, almost pure solute may be present if the nebulization is continued long enough

Experimental Observations

Methods To establish the magnitude of the humidity produced by nebulizers and to test the practical effect of some of the above factors, several different large and small nebulizers were tested at various flow rates and at room temperatures of 25-29° C, under the following circumstances

1 Used directly, without intervening apparatus

2 Used through a "mask" (3″ of 1 1/2″ rubber tubing) with rebreathing bag and non-return valve

3 Used through 30″ of corrugated anesthesia tubing

4 Directed into a sealed enclosure (plastic head tent) of about 3 cu ft capacity

5 Recirculating air within the plastic head tent

6 Directed into one nostril and out the other with the nasopharynx held closed

The nebulizers tested were Type (A) Mist-O_2-Gen "JR", Type (B) NCG Model 24650, Type (C) NCG Model 24850, Type (D) Mist-O_2-Gen "SR", Type (E) Vaponefrin (E_1 and E_2-Model "500," E_3-Model "Standard"), Type (F) Adrenomist, and Type (G) DeVilbis No 40

Total humidity of nebulizer output was measured by standard wet and dry bulb thermometry techniques[9] after warming the entire stream to above the dew point of the mist Vapor humidity at any location was obtained from a temperature reading, liquid humidity at that location was the difference between total and vapor humidity When the mist passed through apparatus before measurement, the difference represented *effective* liquid humidity since it did not include any un-evaporated liquid lost in the apparatus

Observations were converted to per cent B H by first determining pH_2O from vapor pressure and psychometric data[10] and then using the relation between pH_2O and per cent B H explained above Wet and dry bulb observations were initially checked by dew point readings, this was discontinued when general agreement was found Reliability of the data was indicated by agreement within 1-2 per cent B H of several readings taken during long runs on the large nebulizers while warming of the output stream was varied so that wet-dry bulb difference ranged from 2-15° C

Results All the observations made are listed in Table I Table II summarizes the ranges of liquid and total humidity encountered under the various circumstances of the study and compares these values with data on humidity produced by various devices recalculated from observations by previous investigators

In Figure 1 the various humidities are plotted as per cent B H against operating temperature The saturated vapor curve indicates the *vapor*

TABLE I
NEBULIZER HUMIDITY PRODUCTION

Nebulizer Type	Nebulizer No	Nebulizer Operation: Flow Rate, L/Min: To Mixed	Nebulizer Operation: Flow Rate, L/Min: Jet	Nebulizer Operation: Temperature: Room	Nebulizer Operation: Temperature: At Nebulizer [A]	Nebulizer Operation: Temperature: At Delivery [A]	Humidity Produced, Per Cent B H: Liquid: At Nebulizer [B]	Humidity Produced, Per Cent B H: Liquid: At Delivery	Humidity Produced, Per Cent B H: Total
LARGE CONTINUOUS DUTY NEBULIZERS									
A	1 to 11	Direct	10	25 5 to 26 5	16 to 17		6 to 23		35 to 52
		Direct	10	26 0	16 5		14		43
			15	27 5	15 3		10		37
	4	Tube	15	27 0	15 0	19 1	(12)	5	38
			15	26 2	14 0	17 1	(9)	4	33
			15	27 0	14 0	16 1	(8)	4	32
			15	27 0	13 5	15 5	(5)	2	29
			15	27 0	13 1	15 1	(3)	0	26
			15	27 0	16 1	17 2	(3)	1	31
		Recirculating	10	25 7	22 5	23 8	(6)	2	48
			15	25 7	22 0	23 5	(6)	2	47
B		Tube	15	27	15 5	19 8	(19)	11	46
			20	26 5	14 3	17 8	(12)	6	37
			30	25 5	12 9	16 1	(10)	5	33
		Tent via Tube	15	26	19 5[C]	25 0	(14)[C]	0	49
			20	26	18 0[C]	24 3	(15)[C]	0	47
			30	26	16 0[C]	23 4	(16)[C]	0	44
C		Tube	15	26 5	15 0	19 7	(22)	13	48
		Tent	15	27 0	15 5	24 7	(22)	1	49
D		Tube	9	25 5	18 5	22 0	(26)	17	58
			10	25 5	18 9	21 0	(24)	20	57
			5 0	25 0	20	22 6	(21)	15	51
		Tent	10	25 5	18 6	25 0	(18)	2	51
SMALL NEBULIZERS									
E	2	Direct	5	28 0	15 2		44		70
	1		8	29 0	15 5		57		84
	2		13	28 7	15 5		54		81
	3		13	28 5	13 9		49		73
	2	Mask	11	29 5		17 5		10	41
	3		11	29 5		17 8		9	40
	2	Tube	11	29 0	13 0	22 3	(57)	38	80
	3		11	28 7	12 5	22 2	(54)	35	76
	2	Tent	9	27 0	14 0	25 0	(34)	9	58
	2	[D]	11		12 3	13 5	(55)		77
F		Direct	16	28 5	13 5		26		50
		Mask	16	29 0		17 5		5	36

TABLE I NEBULIZER HUMIDITY PRODUCTION—Continued

G	Direct	20	28 5	13 2		21		48
1	Tube	17	28 7	13 0	20 0	(31)	18	54
	Mask	3	29 0		17 3		23	53
		16	29 0		16 7		20	49
		20	29 0		16 0		18	46
	Tent	12	26 5	14 2	24 5	(26)	4	51
		16	26 5	13 4	24 3	(28)	5	52
		20	26 5	12 7	24 0	(28)	4	50
2	Direct	10	31	15 5		29		56
	Nasal[E]	10	31	15 5	31 2[E]		8[E]	76[E]

[A]—Read vapor humidity from Fig 1
[B]—Brackets indicate effective liquid humidity
[C]—R A —Room air admixed
[D]—Directed through nebulizer Type A
[E]—Directed through the nostril, output measured from other nostril

TABLE II
RANGE OF HUMIDITY VALUES

Device and Operation		Gas Flow Rate L/Min	Operating Temperature °C	Warming in Apparatus °C	Liquid Humidity At Nebulizer % B H	Liquid Humidity At Delivery % B H	Liquid Humidity Total Humidity % B H
Nebulizer Direct	(A 1-11)	10-15	15-17		6-23		35-52
	(D,F,G)	5-20	13-15		21-57		48-84
Nebulizer by Tube	(A,B,C,D)	15-85	13-20	1-5	3-26	0-20	26-58
	(E,G)	11-16	12-13	7-10	31-57	18-38	5480
Nebulizer Through "Mask"	(E,F,G)	11-20		4-5		5-23	36-53
Nebulizer Into Tent	(B,C,D)	10-30	15-19	To near	14-22	0-2	44-51
	(E,G)	9-20	13-14	Room temp	26-34	4-9	50-58
Nebulizer Recirculating	(A)	10-15	22	To near Room temp	6	2	47-48
Nebulizer Through Nose	(G)	10	15 5	15 7	29	8	
"Natural fog"[11]			24			5-17	51-63
Nebulizer in Incubator[1]			31-32			3-11	79-83
Airway "Exchanger"[-]			26-27			?	70-80
Water evaporator[1]		35-20	49			0	80-89
Oxygen bubblers[15 1]		3	46			0	60-70 R H *
						0	86

*R H = Relative Humidity

humidity at any operating temperature, whereas data on total humidity is indicated by the various lines and points The height of the total humidity above the vapor curve indicates the *liquid humidity* The lined area of Figure 1 represents all the data for actual or effective liquid humidity production at the nebulizer except for nebulizer type (E) which is represented by the points high above the curve With this exception, total humidity production was about 30-60 per cent B H and liquid humidity about 5-30 per cent B H The points near the vapor curve at 25° C represent the values sampled from the tent as well as data from the literature on "natural fog" in a room,[11] the points at 31 5° C are the data from the literature on incubator mist content [12] It will be noted that the amounts of liquid humidity are ordinarily small in relation to 100 per cent B H, although they provide an important increase over the vapor humidity that can be obtained at comfortable room temperatures Therefore, variations in mist production are not as significant as might be expected in the production of near body humidity, operating temperature is a more important variable The extension of the line in Fig 1 representing mist containing 15 per cent liquid humidity is based on the assumption that liquid content is independent of operating temperature The general validity of this assumption is confirmed by the observation that mist production from a heated nebulizer seems to be as copious as that from an unheated nebulizer The vapor humidity curve and such a line representing additional liquid humidity permit estimation of the temperature to which a nebulizer must be heated to provide near body humidity Fig 1 also provides a convenient means

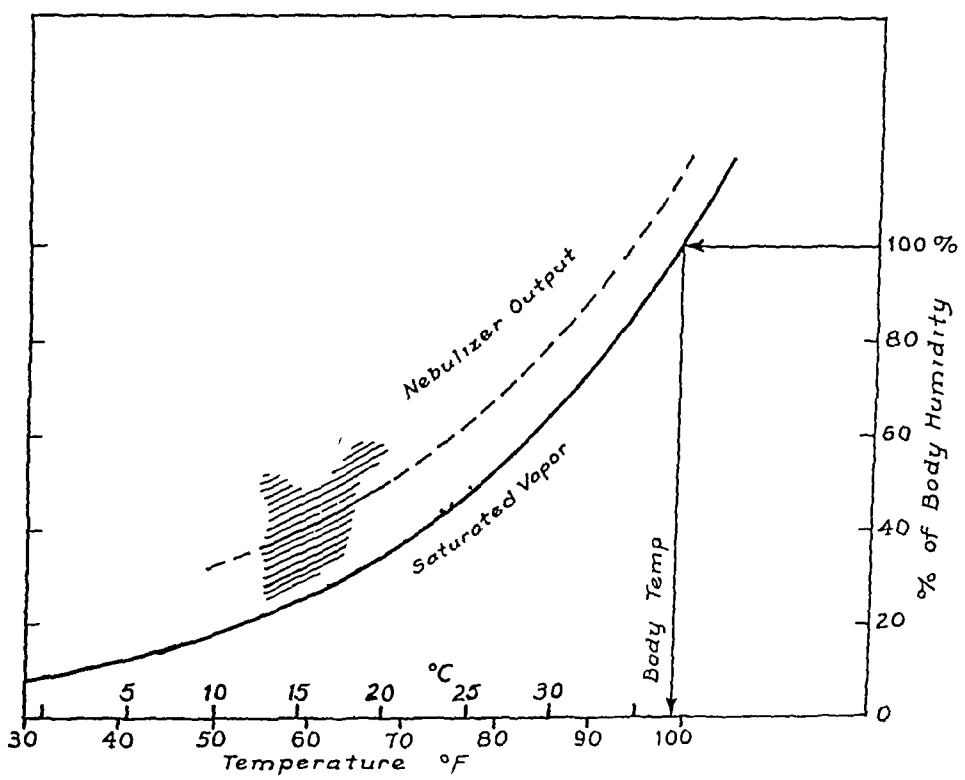


FIGURE 1 Humidity—Temperature relations for nebulization of H_2O

of visualizing other humidities The per cent B H of any air is obtained by multiplying the value from the saturated vapor curve at the temperature of the air by the fractional relative humidity

Discussion

Except for nebulizer type (E), very little loss in humidity resulted from baffling or raining out in the tube or tent This is shown by a few comparisons between liquid output in direct use and effective liquid output in direct use through the tube or tent at similar operating conditions in Table I In confirmation, little water collection was noted in the apparatus, even during long runs This means that the number of large particles produced by these nebulizers and baffled out in the apparatus did not exceed the ability of the apparatus to evaporate liquid collected on the surface at these room temperatures

As shown by Tables I and II, warming of the mist stream in the apparatus ranged from 1-10° C in the tubing depending on flow rate and mist-room temperature difference Warming in the mask was evidently about 4 5° C and the mist was warmed to within 1 2° of room temperature in the tent This, together with the associated data on fall in liquid humidity, indicates the degree of conversion of liquid to vapor humidity that can be expected in practice

The liquid humidities sampled from the tent are low even for nebulizer type (E), which covered the floor with water, as are values obtained from the literature Apparently, as pointed out by Arnold and Tovell,[11] it is difficult to maintain high liquid humidity in an enclosure

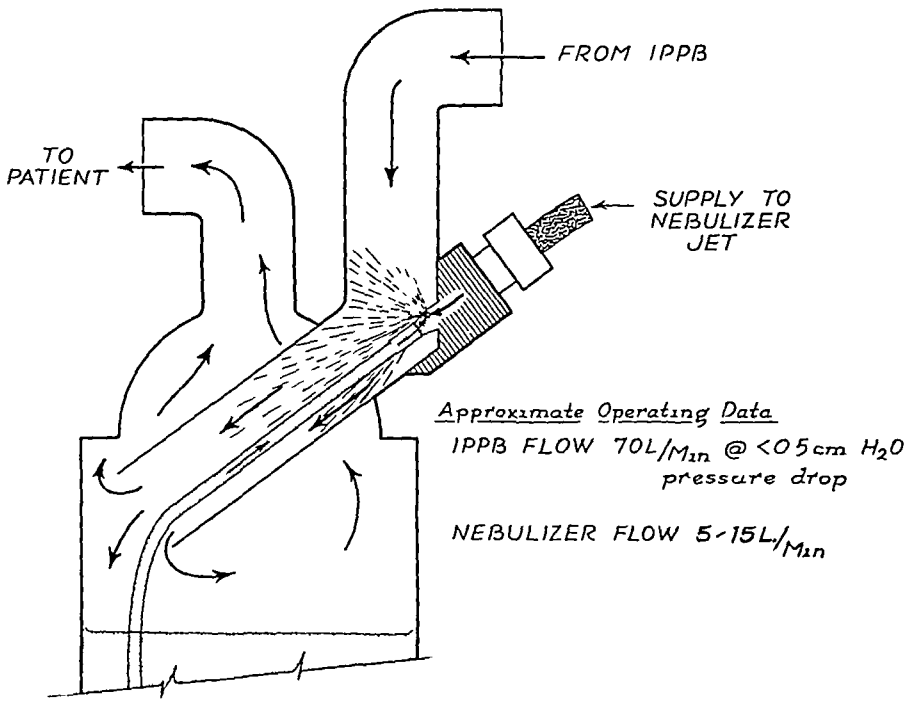


FIGURE 2 Mainstream nebulizer operation

As shown by the data for nebulizers type (A) and (B) (Table I), liquid humidity production falls at high flow rates However, liquid humidity was still produced by nebulizer type (A) at a dry gas flow rate of 85 L/min

The effect of pre-existing humidity in the air stream to the nebulizer is shown most strikingly by the test of recirculation within an enclosure (Nebulizer type (A), Tables I and II) Operating temperature rose from a usual 15° C to 22° C and total humidity rose 10 per cent B H above any previous value for this nebulizer Recirculation, by taking advantage of heating from the room and patient, produces the highest possible humidity from an unheated nebulizer Room air admixing, although the data are obscured by high flow rate, also shows a rise in operating temperature

When warming of mist in the airways was simulated by directing mist from nebulizer type (G) through one nostril and measuring as it emerged from the other (Tables I and II), liquid humidity dropped from about 30 per cent to about 10 per cent B H Whether this was because of baffling or warming is not known At any rate, the amount of pure water liquid humidity reaching the lower airways may be much less than that delivered to the patient

Nebulizer type (E) deserves special comment It produced liquid humidities well above that of the other types, even when its output was passed through the baffle system of nebulizer type (A) It seems an excellent choice for side stream nebulization of IPPB assistors (see next section) if kept full and operated at maximum flow rate The high humidity produced was partially dependent on this "over loaded" operation Under other conditions it was not much more effective than other nebulizers, for instance, its normal flow rate was less and its effective humidity dropped sharply in mask or tent The performance of this nebulizer is particularly significant because it indicates that nebulizers can be built to produce very high liquid humidity

All of the above results concern the nebulization of pure water However, a few comparisons of water and detergent solution nebulization under identical operating conditions showed no significant difference in amount of liquid leaving the nebulizers

The clinically important conclusions of the observations in light of previous information are

1 Oxygen bubblers, especially if heated, and suitable air conditioning equipment[9] should provide near the 70 per cent relative humidity which is sufficient to prevent subjective symptoms in patients with normal airways and breathing patterns

2 Cold nebulization provides the level of humidity necessary to prevent drying of the tracheo-bronchial tree except under the most adverse conditions However, much of its clinical effect must be due to medication rather than humidification

---

[9] Alevaire ®

3 Significantly higher humidities are obtained when a cold nebulizer is used to recirculate air in an enclosure than by other methods of cold nebulization

4 To assure significant deposition of pure water in the lower airways, or to provide near 100 per cent body humidity for tracheostomy breathing, the operating temperature of most nebulizers must be raised by some form of heating

Humidification for IPPB

IPPB assistance with completely dry gas has maximum drying effect because of a combination of factors Administration is often through the mouth or tracheostomy, large tidal volumes and hyperventilation are common, and the usual subject is susceptible to drying because of pulmonary disease or serious illness Without any humidification, significant drying may result even from short periods of IPPB assistance, for instance if the patient does not wet his mouth

Humidification by the usual small side-stream nebulizer is sufficient to prevent drying during intermittent use of IPPB, especially if medication to thin secretions is included On the average, such nebulization may provide 10 L/min of nebulizer gas at 50 to 75 per cent B H which when mixed with dry gas flowing at a mean rate of 40 L/min during inspiration,[13] produces a mixture of 50 L/min at 12 to 20 per cent B H , effective humidity is raised above these values by the amount of completely nebulized gas which collects in connecting tubing during expiration The result is gas which approximates ordinary room air temperature and humidity Under other circumstances, however, negligible humidity may be produced Patients frequently inspire at mean rates of 70 to 80 L/min with peak instantaneous flow rates up to 100 L/min [13] Also, nebulizers may be slightly defective, and the nebulizer pressure tubing may not permit high nebulized gas flow rates This may result, for example, in 5 L/min of 50 per cent B H being mixed with 75 L/min of dry gas to give only 3 per cent B H

When IPPB is used continuously, side stream nebulization is inadequate Patients requiring such treatment cannot usually tolerate drying, and even slight drying effect may become significant if continued long enough The small nebulizers quickly run dry and frequently plug, while continuous duty nebulizers produce somewhat lower humidity The humidification provided by side stream nebulization is obviously inadequate for use with tracheostomy

Adequate humidity for continuous IPPB assistance can be assured if *the entire output of dry gas from the assistor passes through the contacting* chamber of a nebulizer (*mainstream nebulization*) This is conveniently accomplished by connecting the room air admixing port of a suitable continuous duty nebulizer to the outlet connection of the IPPB assistor * Operation of such a device is illustrated in Fig 2 A spray

*Available through Mist-O-Gen Equipment Company, Oakland, California

of liquid is produced by a jet of high pressure gas in the usual manner, the entire flow from the assistor is mixed with this spray in the contacting chamber, and the resulting combined stream is then baffled and passed to the patient in the usual manner The entire output is completely nebulized even at high flow rates, as shown by the data (Neb A, Table I) on a nebulizer used for mainstream nebulization, and the observation that a visible mist is delivered to the patient Heating the nebulizer provides any humidity desired, and this is easily accomplished by setting the nebulizer in a pan of water heated on a hot plate [4]

The resistance added to the circuit is small, amounting to less than 0 5 mm Hg pressure drop at high flow rates, partly because of the aspirating effect of the jet This effect, amounting to a negative pressure of 1-2 mm Hg at the assistor during expiration, has only a slight effect on operation of the pressure sensitive patient demand valves of some types of assistors

Such devices have been in general use on our wards for over a year They have made possible the routine use of IPPB assistors as respirators on the polio ward and elsewhere In general, the nebulizer is used unheated for continuous naso-oral administration and is heated to near body temperature for tracheal administration or when dried out secretions are present

More adequate humidity can also be obtained in the usual side arm nebulization method by adding a larger volume, say about 1 liter, to the tubing between the assistor and the exhalation valve This is filled with nebulized gas during expiration A continuous duty nebulizer is desirable, and it can be heated if necessary to obtain higher humidity

SUMMARY

Available information plus knowledge of the physical processes involved in respiratory air conditioning provide a rational basis for the use of therapeutic humidification Definite indications for humidification of dry air include gross drying of the upper airways, respiration by tracheostomy, and the presence of thick tracheo-bronchial exudate or decreased ability to move exudate and secretions through the trachea Medication may be important in the treatment of airway drying, but its effects should not be confused with that of humidification

With one exception, the nebulizers tested were found to produce total humidities of 30 to 60 per cent B H , this seems sufficient for most therapeutic needs If near body humidity is required, nebulizers must be heated Some of the variables concerned with final liquid humidity delivery in nebulization are design, gas flow rate, apparatus used for delivery, and the patients' airways

The usual side stream nebulization technique is not adequate in continuous IPPB assistance A mainstream nebulization technique which provides adequate humidity is described

The convenient absolute humidity expression "per cent body humidity" is proposed for use in respiratory physiology

Extension of experimental work and further application of evaporative process principles to respiratory air conditioning in disease states are indicated to confirm and amplify the conclusions of this study Further knowledge of the humidity provided in various inhalation therapy situations would be desirable

RESUMEN

La información obtenible además del conocimiento de los procesos fisiológicos que existen en el aire respiratorio, dan una base racional para el uso de la humidificación terapéutica Las indicaciones definidas de la humidificación incluyen gran sequedad de las vías respiratorias superiores, respiración por traqueostomía y la presencia de exudado traqueobronquial o la capacidad deficiente para expulsar las secreciones por la tráquea La medicación puede ser importante en el tratamiento de sequedad de las vias respiratorias pero no deben confudirse sus fectos con la humidificacion

Con excepción de uno, los nebulizadores probados produjeron humedades totales de 30 a 60 por ciento B H , esto parece suficiente para la mayoría de las necesidades terapéuticas Si se requieren humedades como las corporales los nebulizadores deben calentarse Algunas de las variantes relativas al rendimiento de humedad en la nebulización son construcción, velocidad de paso, aparatos usados para proporcionar el paso y las condiciones de las vías respiratorias

La nebulización por corriente lateral no es adecuada para la atencion por el aparato de IPPB Se describe una nebulización por medio de la corriente principal

La expresión de humedad absoluta "por ciento de humedad" se propone para usarse en fisiología respiratoria

Están indicadas, para confirmar y ampliar las conclusiones de este estudio la *extensión del estudio experimental y la ulterior aplicación* de los principios de los procesos de la evaporación al acondicionamiento del aire respiratorio

Es de desearse mayor conocimiento de la humedad que se proporciona en varias circunstancias de inhalación

RESUME

Une documentation valable ainsi que la connaissance des processus physiques que comportent les conditions de l'air respiratoire constituent une base logique pour utiliser l'humidification thérapeutique Les indications précises pour l'humidification de l'air sont l'asséchement important des voies respiratoires supérieures, la respiration par trachéostomie, et la presence d'exsudats trachéo-bronchiques épais, ou la diminution de la possibilité de rejeter les exsudats et sécrétions par la trachée Les médications peuvent *avoir une action importante dans le traitement* de l'asséchement des voies respiratoires mais ses effets ne doivent pas être confondus avec ceux de l'humidification

Sauf une exception, il s'avéra que les nébulisateurs étudiés produisaient

des humidités totales de 30 à 60% de l'humidité du corps humain, ce qui semble suffisant pour la plupart des nécessités thérapeutiques S'il faut obtenir une humidité voisine de celle necessaire au corps humain, les nébulisateurs doivent être chauffés Quelques-uns des éléments qui conditionnent la variabilité du degré final de l'humidité projetée par le nébulisateur sont le modèle, le taux du débit du gaz, l'appareil utilisé pour la production, et les voies respiratoires du malade

La technique habituelle de nébulisation avec production de vapeur n'est pas adaptée à un traitement continu

Une technique de nébulisation susceptible de produire une humidite convenable est décrite

L'emploi de l'expression d'humidite absolue "en pourcentage d'humidité humaine" est proposée pour la physiologie respiratoire

Un complément du travail expérimental et une application ultérieure des principes du processus d'évaporation appliqué a la climatisation de l'air respiratoire dans les états pathologiques sont indiqués pour confirmer et amplifier les conclusions de cette étude Il serait désirable de connaitre par des études ultérieures l'humidité fournie dans différentes situations de la thérapeutique inhalatoire

ZUSAMMENFASSUNG

Brauchbare Information und Kenntnis der physgalischen Vorgange, die bei der respiratorischen Klimatisierung beteiligt sind, bieten Gewahr fur eine rationale Basis bei der Anwendung der therapeutischen Feuchtigkeitsregulierung Absolute Indikationen fur die Feuchtigkeitsregulierung eines trockenen Luftraumes umfassen starke Austrocknung der oberen Luftwegen, Atmung durch Tracheotomie und das Vorliegen von zahem tracheo-bronchialem Exsudat oder vermindertes Vermogen, Exsudat und Sekret durch die Trachea zu bewegen Interne Behandlung kann wichtig sein in der Therapie der trockenen Luftwege, aber ihre Wirkungen darf man nicht verwechseln mit denjenigen der Feuchtigkeitsregulierung

Es ergab sich mit einer Ausnahme, dass die gepruften Vernebelungsgerate imstande waren, totale Feuchtigkeitswerte von 30-60% Korperfeuchtigkeit zu erzeugen, dies erscheint ausreichend fur die meisten therapeutischen Bedurfnisse Wenn der Korperfeuchtigkeit naher liegende Werte verlangt werden mussen die Vernebelungsgerate erhitzt werden Einige der veranderlichen Grossen, die mit der endgultigen Lieferung von flussiger Luftfeuchtigkeit bei der Vernebelung zusammenhangen sind Bauart, Ausmass der Gasstromung, fur die Abgabe benutzte Apparatur und die Luftwege des Kranken

Die gewohnliche Technik der Seitenstromvernebelung ist nicht geeignet zur fortlaufenden IPPB—Assistenz Beschreibung einer Vernebelungstechnik im Hauptstrom, die Gewahr bietet fur eine adequate Feuchtigkeitsabgabe Die geeignete Bezeishnung der absoluten Feuchtigkeit in "Prozent Korperfeuchtigkeit" wird zur Verwendung fur die Physiologie der Respirationsorgane vorgeschlagen

Ausdehnung der experimentellen Arbeit und weitergehende Anwendung der Grundsatze der Verdampfungsprozesse auf die Klimatisierung bei der Atmung bei Krankheiten sind angezeigt zur Bestatigung und Erweiterung der Schlussfolgerung dieser Untersuchung Weitere Kenntnis der Feuchtigkeitsgrade, die bei verschiedenartiger Situation von Inhalationstherapie verordnet werden, ware wunschenswert

REFERENCES

1 Walley, R V "*Humidifier for Use with Tracheotomy and Positive Pressure Respiration*," *Lancet*, 1 781, 1956

2 Marshall, J and Spalding, J M K "Humidification in Positive-Pressure Respiration for Bulbospinal Paralysis," *Lancet*, 2 1022, 1953

3 Cole, P "Further Observations on the Conditioning of Respiratory Air," *J Laryng and Otol*, 67 669, 1953

4 Ingelstedt, S "Studies on the Conditioning of Air in the Respiratory Tract," *Acta Oto-Laryng Suppl* 131, 1956

5 Heetderks, D R "Observations on Reaction of Normal Nasal Mucous Membrane," *Am J M Sc*, 174 231, 1927

6 Dalhamn, T "Mucous Flow and Ciliary Activity in the Trachea of Healthy Rats and Rats Exposed to Respiratory Irritant Gases," *Acta Physiol Scandinav*, 36 Suppl 23, 1956

7 Rohrer, F "Der Stromungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmassigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in Verschiedenen Lungenbezirken," *Arch f d ges Physio*, 162 225, 1915

8 Abramson, H A, in *Treatment of Asthma*, edited by Abramson, H A, Williams and Wilkins Co, Baltimore, 1951

9 *Chemical Engineer's Handbook*, edited by Perry, J H, Third Edition, McGraw-Hill Book Co, New York, 1951

10 *Handbook of Chemistry and Physics*, edited by Hodgman, C D, 37th Edition, Chemical Rubber Pub Co, Cleveland, O, 1955

11 Arnold, G T, and Tovell, R M "The Production of Fog as a Therapeutic Agent," *Anesthesiology*, 17 400, 1956

12 O'Brian, D, Hansen, J D L and Smith C A "Effect of Supersaturated Atmospheres on Insensible Water Loss in the Newborn Infant," *Pediatrics*, 13 126, 1954

13 Wu, N and Cushing, I E Uupublished data

14 Miller, W F, Cade, J R and Cushing, I E "Preoperative Recognition and Treatment of Bronchopulmonary Disease," *Anesthesiology*, in press, 1957

15 Sandove, M S, Miller C E and Shima, A T "Postoperative Aerosol Therapy," *J A M A*, 156 759, 1954

Temporary Collapse in the Treatment of Pulmonary Tuberculosis

F T ROQUE, LT COL, MC, F C C P
Denver, Colorado

The past decade marked the beginning of the era of chemotherapy of tuberculosis and more progress in the treatment of this disease was made than in all the years prior to 1946 when streptomycin was first introduced Other anti-tuberculosis drugs of proved value such as Isoniazid (INH), Para-aminosalicylic Acid (PAS), Viomycin (VM), Pyrazinamide (PZA) and Cycloserine (CS) came into the armamentarium of phthisiologists and were initially used alone and later in combinations It should be noted that coincidentally, advances in anesthesiology and surgery of the lungs were accomplished Chemotherapy and resectional surgery in the therapy of tuberculosis were born and apparently are here to stay

In the meantime, the old standby and friend, temporary collapse, suffered in its use and seems doomed to extinction There are those who still advocate the use of artificial pneumothorax, pneumoperitoneum and phrenemphraxia In a recent tour in Europe, I noted the widespread popularity of these procedures in Germany, France and England This is reflected in their current literature which contains frequent reports on results of pneumotherapy, in contrast, only occasional reports appear in American literature Scadding[1] of Brompton Hospital, London, in his recent Lettsomian Lectures emphasized the important place of artificial pneumothorax, phrenic paralysis and pneumoperitoneum with and without anti-bacterial treatment Ellman, et al,[2] report that even without chemotherapy, good results may be anticipated from artificial pneumothorax, provided cases are carefully selected

In this paper, it is my purpose to report the changing concept and status of temporary collapse in the past 10 years at Fitzsimons Army Hospital and my own view based on experence since 1933

Rest is generally accepted as fundamental in the treatment of pulmonary tuberculosis Tuberculosis sanatoria were established in all countries in the world to provide a haven of rest for those afflicted with the disease as well as to segregate them from the general population It may be mentioned that the concept of rest[3] is at present being challenged as to its necessity Temporary collapse measures, namely, artificial pneumothorax, pneumoperitoneum, phrenic nerve paralysis and combinations of pneumoperitoneum and phrenemphraxia, basically are attempts to secure rest by so-called "splint" or "selective collapse" of diseased lungs This is the *raison d'etre* of collapse therapy

Artificial Pneumothorax

In 1888 Carlo Forlanini first introduced pneumothorax in the treatment of pulmonary tuberculosis Since then, the procedure gained in-

*From the Pulmonary Disease Service, Fitzsimons Army Hospital

creasing use until recent years It took about 30 years for others to follow and in the United States and Asiatic countries, the peak of its popularity occurred in the 30's and 40's This was only to be expected as the procedure was not only theoretically attractive but also provided the first effective weapon besides bed rest to be placed in the hands of the phthisiologist Here, at long last, was something real, tangible and concrete that medical men could offer the afflicted, a sort of positive hope for the hopeless In the early years it was employed only in unilateral cases which did not respond fast enough after three to six months of bed rest It did not take long before therapeutic pneumothorax was used in practically all cases of pulmonary tuberculosis regardless of extent of disease—minimal, moderately advanced or even far advanced Later, bilateral pneumothorax also came into use

In retrospect, I shudder to think of not only the misuse but the abuse of this procedure Practically every medical man learned how to induce pneumothorax How many of us used to delight in the early conversion of some cases with positive sputa to negative, thus sending patients away from the sanatorium much sooner than mere bed rest permitted us in the past Specifically, did we enjoy seeing "bread-winners" return to their work and thus become useful individuals again All the patient had to do was to return for refills each week, twice a month or even once a month Of course the vast majority of these patients had to be re-hospitalized because of relapse, contralateral spreads and/or reactivation of the disease, empyema, etc , and in the end—death The few who did not relapse had to be "refilled" for years (my longest was 12 years) for nobody knew when to stop In many cases the pneumothorax was discontinued because there was not available a needle long enough to reach the pleural space At the annual meeting, American College of Chest Physicians in San Francisco in 1954, at a panel discussion on pneumothorax, the consensus of opinion was that the best type of pneumothorax should be terminated after two years In this same meeting, I expressed the opinion that pneumothorax as a weapon against pulmonary tuberculosis was and always will be a poor one and therefore should be forgotten *There no longer exists any indication for its use because the lesions which in the past have responded so well to pneumothorax are also the very type which respond so remarkably well with chemotherapy*

In 1951, Mitchell[4] published six reports wherein he analyzed 557 cases of pneumothorax successfully induced over a decade (1930-1939) at Trudeau Sanatorium He recommended the following rules in the management of pneumothorax

1 Free anatomic collapse should be achieved or the pneumothorax abandoned

2 Sudden persistent contraction and airlessness of a lobe or lung soon after induction is strong indication for abandonment of pneumothorax and consideration of some other type of procedure

3 If cavity closure and sputum conversion do not occur within 3 to 4

months, abandonment and alternative forms of treatment should be seriously considered

4 Abandonment of pneumothorax should be seriously considered if fluid sufficient to hide the hemidiaphragam continues to form a month or longer Abandonment and prompt obliteration of the pneumothorax space is strongly indicated at the first sign of cloudy, purulent fluid or bacteriological evidence that the fluid is secondarily infected

I personally endorse the above rules of management However, I would like to point out that it would be difficult to find 10 out of 100 induced pneumothoraces which would not be abandoned after six to eight months if we were to follow the rules as suggested by Mitchell So why should anybody start a pneumothorax at all and take the risk of complications? Some of the common complications of pneumothorax are

1 Adhesions—50 to 75 per cent of all induced pneumothoraces will have varying degrees of pleural adhesions A small percentage may be amenable to intrapleural pneumonolysis

2 Effusion—pleural fluid will develop in a few days to six months in 70 to 80 per cent of all cases Empyema will result in the majority of these cases.

3 Tension cavities—a not too infrequent occurrence

4 Spread of disease—on the same and/or contralateral side

5 Atelectasis of a lobe or more

6 Fibrothorax and/or non-expandable lung

7 Mediastinal hernia

8 Air embolism—which may be severe enough to be fatal

9 Subcutaneous ephysema—escape of air into the subcutaneous space may be so severe as to involve the chest, neck and face or may extend down to abdomen and lower extremities

TABLE I

	PNEUMOTHORAX		PNEUMOPERITONEUM		PHRENEMPHRAXIA
Year	Initial	Refills	Initial	Refills	
1946	564	22,484	0	0	210
1947	264	11,784	123	4,493	114
1948	294	4,548	132	3,190	60
1949	150	3,368	319	6,319	37
1950	317	2,491	640	12,529	36
1951	34	1,067	660	14,350	46
1952	4	334	572	18,793	15
1953	0	32	98	5,501	0
1954	0	0	0	0	0
1955	0	0	0	0	0

The pneumoperitoneums initiated in 1954 and 1955 were performed only as space filling procedures following lower lobe resections

10 Perforation of blood vessels—resulting in hemorrhage into pleural cavity

11 Perforation of the lung—usually on initiation of pneumothorax and may also occur anytime during refills

At Fitzsimons Army Hospital, therefore, therapeutic pneumothorax was completely abandoned in 1953 as a definitive procedure in the management of pulmonary tuberculosis (Table I)

Pneumoperitoneum

Pneumoperitoneum was introduced by Banyai in 1931 The partial collapse of the lung so obtained seems to exert beneficial effect on pulmonary tuberculosis similar to that obtained in pneumothorax The popularity of pneumoperitoneum increased in the decade preceding the era of chemotherapy and recently, according to Trimble,[5] has largely replaced pneumothorax For many years it was principally used in cases of bilateral tuberculosis and of unilateral lower lobe tuberculosis Later, even unilateral upper lobe disease was treated with pneumoperitoneum coupled with phrenic nerve paralysis on the same side as it was found that impairment of pulmonary function resulting from collapse of lungs by pneumoperitoneum was only minimal The complications of pneumoperitoneum, although less than in pneumothorax, are still numerous We quote the following from a report of Bobrowitz[6] as a good list of the complications of pneumoperitoneum

A Thoracic Complications
- 1 Mediastinal emphysema
- 2 Pneumothorax
- 3 Bronchial obstruction and atelectasis
- 4 Marked pulmonary collapse

B Complications Due to Administration of Air
- 1 Air embolism
- 2 Subcutaneous emphysema
- 3 Febrile response
- 4 Pain

C Abdominal Complications
- 1 Adhesions
- 2 Peritoneal fluid
- 3 Intestinal obstruction
- 4 Gastrointestinal symptoms and anatomic changes
- 5 Acute appendicitis
- 6 Tuberculous peritonitis
- 7 Non-tuberculous peritonitis
- 8 Peritoneal insult or mechanical peritonitis

D Complications of Abdominal Wall
- 1 Hernia

E Vascular Pressure
- 1 Lower extremity edema

The indications of pneumoperitoneum are basically the same as that of pneumothorax, however, patient acceptance of it is rather inferior to that of pneumothorax Therefore, the use of this procedure has, like that of pneumothorax, become less and less popular with the success obtained with chemotherapy and resectional surgery of residuals I agree also with Livingstone[7] of England who last year stated that he has never used pneumoperitoneum without temporary phrenic paralysis, which, *per se*, limits its usefulness to selected unilateral cases Furthermore, the duration of pneumoperitoneum therapy is rather prolonged—2 to 5 years At Fitzsimons Army Hospital, pneumoperitoneum reached its peak in 1951 and 1952 only to be practically abandoned in 1954 (Table I), because of the more desirable results obtained by the use of chemotherapy and resection of serious residuals At present I use pneumoperitoneum only in those rare and extreme cases in which residual lesions, after prolonged chemotherapy, cannot be excised because of serious impairment of pulmonary function that would result if extensive surgery were performed

Phrenic Nerve Paralysis

Phrenic nerve paralysis in the treatment of pulmonary tuberculosis was first proposed by Stuertz in 1911 for severe unilateral tuberculosis of the lower lobe of the lung Sauerbruch, however, first performed this operation in 1904 in animal experimentation and indicated that the rest and collapse of the lung induced by hemidiaphragmatic paralysis favored healing This work was supported by Schepelmann in 1913 who stated that even apical tuberculosis was benefited by this operation

The popularity of phrenic nerve operations has varied since these procedures were first introduced Although its use initially was limited mainly to treatment of lower lobe disease and as a supplement to bed rest in the treatment of minimal apical disease, these procedures have been further limited in their application by the advent of chemotherapy which in most cases has eradicated its use in the treatment of minimal disease The operations first introduced were of a permanent collapse type (phrenic exeresis or phrenicectomy), but temporary paralysis of the hemidiaphragm (phrenemphraxis) is now generally preferred Supplementary to pneumoperitoneum, its specific purpose is simply to increase the rise of the

TABLE II

Year	Pts Treated to Inactive Stage	Pts Treated with Chemo Rx Alone in Per Cent	Pts Treated with Chemo and Temp Collapse in Per Cent	Pts Treated with Chemo & Surgery in Per Cent	Pts Treated with Rest Alone in Per Cent
1952	431	22 8	53 6	22 5	1 1
1953	527	42 0	28 0	30 0	0 0
1954	469	57 2	0 0	42 8	0 0
1955	397	51 9	0 0	48 1	0 0

Note The decrease of patients in 1955 was due to reduction of beds for tuberculosis

diaphragm It often finds its field of usefulness here, especially in lower lobe involvement or in instances where the elevation of the diaphragm is limited after pneumoperitoneum has been induced

The complications and failures of phrenic nerve paralysis consist of

1 Operative complications Damage to other nerves (vagus, sympathetic, etc), vascular structures and thoracic duct may result during the operation These are rare and then usually the result of having an inexperienced operator, or may be due to disturbed relationships which usually are noted in re-crush operations

2 Secondary symptoms Gastric distress, dyspnea, cardiac palpitation, etc , may follow a high rise of the diaphragm, particularly on the left side

3 Failures of the diaphragm to rise after operation

a The presence of anamolous branches or positions of the phrenic nerve, which make it difficult to find and completely crush all branches of the nerve

b The diaphragm may not rise if the lung is bound down by pleural adhesions such as may be present following pleural effusion (this can be avoided if the patient is fluoroscoped to observe movement of the diaphragm prior to recommending the procedure)

c The tone of abdominal muscles may be a factor Lax muscles do not support a continuous intra-abdominal pressure necessary to elevate the diaphragm

4 Permanent paralysis of the hemidiaphragm may occur following phrenemphraxis Reports on the incidence of this vary from 6 to 20 per cent As a result of permanent paralysis of the hemidiaphragm, I have seen in postmortem examinations, atrophied muscle almost as thin as ordinary paper It is therefore quite obvious that in crushing the nerve, care should be exercised so that permanent injury to the nerve does not result This is, however, easier said than done, as there is no instrument which gauges the amount of pressure necessary to crush the nerve This is determined solely on the previous experience of the surgeon

As a primary definitive procedure, phrenic nerve operations were comparatively seldom used at Fitzsimons Army Hospital (Table I) The majority of the 518 cases of phrenic nerve paralysis since 1946 were performed as adjuncts to pneumoperitoneum to obtain further rise of the diaphragm My own experience with phrenemphraxia exceeds the total number done at this hospital in the past decade I shall never forget the years when residents in a sanatorium wagered on who could excise the longest piece of phrenic nerve Those were the days of phrenic exeresis or phrenicectomy Aside from the resulting severely atrophied hemidiaphragm to almost parchment paper thinness, a far worse complication is the development of paradoxical respiration which usually follows when collapse procedures such as thoracoplasty are performed on the contralateral side It is therefore not surprising that operations on the phrenic nerve were dropped at Fitzsimons Army Hospital in 1953

Discussion

The experience at *Fitzsimons Army Hospital* in the overall management of pulmonary tuberculosis points to the importance of chemotherapy and surgical excision of residuals as the principal weapons employed to combat the disease After adequate use of anti-tuberculosis drugs in combinations such as SM-PAS, SM-INH, SM-INH-PAS, INH-PAS, SM-VM, etc, usually after six to eight months, rarely longer, residuals of pulmonary lesions revealed by ordinary postero-anterior roentgenograms, laminograms and/or bronchograms, are excised The amount of diseased lung removed is usually governed by the extent of the residuals and pulmonary reserve the patient has as shown by external and internal pulmonary function tests The above, in brief, is the master plan of treatment of pulmonary tuberculosis at Fitzsimons Army Hospital in the past two years In Table II are the statistics derived from patients treated to the inactive stage at this chest center since 1952 Unfortunately, our research files do not go farther back than 1952 It is most interesting to note that only 1 1 per cent of 431 patients who became well in 1952 were managed with bed rest alone Since then all patients received chemotherapy in addition to rest Furthermore, it is striking to see that in 1952, 53 6 per cent of the patients were managed by chemotherapy and temporary collapse, this figure dropped to 28 per cent in 1952 and to nothing in the past two years Note also that the number of patients who were treated with chemotherapy alone and with drugs plus surgery in 1952 increased roughly by 250 per cent

We would like to point out that the discovery of pulmonary tuberculosis in military personnel is probably much earlier than in most civilian populations The availability of previous chest films from induction centers and routine roentgenograms from outlying military installations, as well as previous medical records, are distinct advantages in the final decision of therapy of each individual patient Therefore, in the great majority of our patients, we are able to determine the duration of the disease process Early discovery and the relatively short morbidity of pulmonary tuberculosis enable us to attain the many "cures" in our hospital by the use of chemotherapy alone and/or surgical excision Temporary collapse procedures have not been used in the overall planning of therapy of pulmonary tuberculosis in the past three years at Fitzsimons Army Hospital

SUMMARY AND CONCLUSIONS

1 The use of temporary collapse procedures—artificial pneumothorax, pneumoperitoneum and phrenic nerve operations was reviewed

2 Artificial pneumothorax and phrenic nerve paralysis are considered obsolete procedures

3 Reversible collapse procedures—pneumotherapy and phrenic nerve paralysis, are no longer considered as primary and/or definitive procedures

4 If, after the adequate use of anti-tuberculosis drugs, cavitary lesions are caseo-nodose residuals which are potentially dangerous to relapse remain, surgical excision is the procedure of choice

5 Pneumoperitoneum may be used only as a last resort in far advanced cases when, after adequate and prolonged chemotherapy, surgical excision of cavities and/or serious residuals cannot be performed because of serious impairment of pulmonary function In those rare patients in whom chemotherapy cannot be used because of severe toxicity, pneumoperitoneum may be considered

RESUMEN

1 Se revisa el uso de procedimientos de colapso temporal (neumotórax, neumoperitoneo y operaciones del frenico)

2 El neumotórax artificial y la parálisis del frénico se consideran procedimientos anticuados

3 Los procedimientos de colapso reversible—neumoterapia y parálisis del frénico—no se consideran ya como procedimientos primarios o definitivos

4 Si después del uso adecuado de las drogas antituberculosas las lesiones cavitarias son caseo-nodosas residuales que son potencialmente peligrosas por las recaídas, el procedimiento de elección es la excisión quirúrgica

5 El neumoperitoneo puede usarse sólo como último recurso en casos extremadamente avanzados cuando, después de adecuada y prolongada quimioterapia no se puede hacer de las cavidades y hay contraindicación a la cirugía por insuficiencia respiratoria En casos en que la quimioterapia no puede usarse por severa toxicidad el neumoperitoneo podría considerarse

RESUME

1 L'auteur passe en revue les procédés de collapsothérapie temporaire (pneumothorax artificiel, pneumopéritoine, interventions sur le nerf phrénique)

2 Il considère le pneumothorax artificiel et la paralysie phrénique comme des moyens périmés

3 Les méthodes de collapsus réversible, pneumothorax et paralysie du nerf phrénique, ne sont plus considérées comme des moyens à utiliser d'emblée et à action indiscutable

4 Si, après emploi correct des médications antituberculeuses, les lésions cavitaires constituent des résidus caséonodulaires qui sont un potentiel dangereux de rechute éventuelle, l'exérèse chirurgicale est le procédé de choix

5 Le pneumopéritoine peut être utilisé en dernier ressort seulement, dans les cas très avancés, lorsque, après chimiothérapie correcte et prolongée, l'exérèse chirurgicale des cavités et des lésions résiduelles graves ne peut être pratiquée par suite de trouble grave de la fonction pulmonaire Dans ces cas limites pour lesquels la chimiothérapie ne peut être utilisée à cause de réactions toxiques qu'elle provoque, le pneumopéritoine peut être pris en considération

ZUSAMMENFASSUNG

1 Die Anwendung von temopären Kollapsmassnahmen kunstlicher Pneumothorax, Pneumoperitoneum und Operationen am Nephren wurden besprochen

2 Der kunstliche Pneumothorax und die Lahmung des Zwerchfellnerven werden als veraltete Massnahmen angesehen

3 Reversible Kollapsmassnahmen—Pneumotherapie und Lahmung des Zwerchfellnerven werden nicht mehr als primare und/oder definitive Massnahmen angesehen

4 Wenn nach dem adaequaten Gebrauch von antituberkulosen Medikamenten kaverndse Veranderungen zu kasig-knotigen Restzustanden werden, die eine potentielle Gefahr zum Rezidiv behalten, ist die chirurgische Excision das Verfahren der Wahl

5 Das Pneumoperitoneum lasst sich nur als letzte Moglichkeit bei weit fortgeschrittenen Fallen anwenden, sofern nach adaequater und langdauernder Chemotherapie die chirurgische Entfernung von Kavernen und/oder erheblichen Resthohlen nicht erfolgen kann wegen erheblicher Schadigung der Lungenfunktion In solchen Fallen, in denen die Chemotherapie nicht zum Einsatz kommen kann infolge schwerer Toxizitat, kann das *Pneumoperitoneum in Erwagung gezogen* werden

REFERENCES

1 Scadding, J G "The Treatment of Pulmonary Tuberculosis," *Lancet*, 269 154, 1955
2 Ellman, P, Johnson, J H P and Kagan, A "The Changing Place of Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis," *Brit J Tubere*, 50 130, 1956
3 Diessler, S H "Changing Attitudes Toward the Therapy of Tuberculosis," *Am Rev Tuberc*, 74 188, 1956
4 Mitchell, R S "Artificial Pneumothorax A Statistical Analysis of 557 Cases Initiated in 1930-1939 and Followed in 1949," *Am Rev Tubere*, 64 151, 1951
5 Trimble, H G "Current Therapy in Pulmonary Tuberculosis in the United States," *Brit M J*, 1 250, 1955
6 Bobrowitz, I D "Complications of Pneumoperitoneum Therapy," *Dis of Chest*, 24 82, 1953
7 Livingstone, J L "Observations in the Treatment of Pulmonary Tuberculosis at the Present Time," *Brit M J*, 1 243, 1955

SECTION ON CARDIOVASCULAR DISEASES

The Application of Hypothermia in the Correction of Cardiovascular Lesions A Study of 140 Cases

EDWARD J JAHNKE, JR , MAJOR, MC, USA
Washington, D C

The concept of lowering body temperature as an adjunct to surgical therapy is not new In a minor way, it has been frequently used to produce temporary tissue insensitivity for incision and drainage of abscesses It has also been applied to decrease toxicity in patients with non-viable extremities who could not tolerate the insult of a major surgical amputation Despite these uses, its value has been at best, insignificant Recently, however, with the great impetus created by the successful correction of previously hopeless cardiovascular lesions, the potential value of hypothermia has been reassessed Its ability to decrease metabolism and thereby permit extended periods of circulatory arrest represented a potential approach to surgery within the cardiac chambers Much work both experimental and clinical, has been accomplished during the last several years From this, hypothermia emerged as a useful tool with application in surgery both inside and outside the heart This report will present our approach to the problem of hypothermia as to first, effects, second, technic and third, clinical application

Effects of Hypothermia

Though hypothermia can extend over a considerable range of temperature variation, this presentation will be concerned with experimental and clinical observations, made during total body cooling from 37 to 24 degrees centigrade It is well documented that the fundamental effect of hypothermia is reduction of the rate of metabolism in all body systems This rate of metabolic slowing is almost linear to approximately 24 degrees centigrade where response is less than 50 per cent of normal Associated with this change are other physiologic alterations which are equally important Among these might be mentioned the decrease in heart rate, stroke volume and cardiac output which result in systemic hypotension and are accompanied by a generalized vasoconstriction There is a rise in blood oxygen saturation which probably reflects decreased utilization and dissociation The respiratory rate falls and may eventually cease If not

From Thoracic Surgery Service, Walter Reed Army Hospital, Washington 12, D C
Presently at San Antonio, Texas

adequately supported, this can result in severe metabolic derangements A progressive neurogenic depression is also observed and may be responsible for some of the serious cardiac irregularities encountered in deep hypothermia

In addition to these effects of hypothermia, many of which are of value in various surgical situations, there are also several inherent and ever present dangers They are first, the onset of significant cardiac rhythm disturbances and second, the development of postoperative hemorrhagic tendencies

We have observed various types of cardiac irregularities The occasional incidence of supraventricular tachycardia or wandering pacemaker cannot be attributed to cooling per se since they are just as likely to occur in the normothermic individual undergoing cardiac surgery On the other hand, atrial fibrillation and, the more serious, ventricular fibrillations are definitely associated with the cooling process Though some observers have reported atrial fibrillations in approximately 50 per cent of patients, our incidence has been insignificant and only noted in patients carried below 26 degrees centigrade These, however, will revert to a normal sinus rhythm on rewarming

Ventricular fibrillation, though a constant concern, has occurred in only seven of 140 or an incidence of 5 per cent In two it developed during anesthesia induction The remaining five were secondary to manual or instrumental manipulation of the heart Its cause has been variously ascribed to a lowering of the myocardial threshold due to cold itself, a sudden change in blood pH, either acidosis or alkalosis, a reduction of serum potassium level or a neurogenic depression and imbalance Regardless of etiology, we have found that slow cooling combined with hyperventilation and gentle cardiac manipulation have kept the incidence at a minimal level In our hands, conversion of a fibrillation occurring during induction in a patient with a large left to right shunt has been a hopeless task despite all types of heroic measures In all other instances, it has been possible to reconvert the heart by a combination of manual cardiac compression and electrical shock No type of drug therapy has been employed Occasionally a patient in deep hypothermia may have to be rewarmed to 26 degrees centigrade for conversion However, this can be rapidly accomplished by constant flushing of the thoracic cavity with warm saline solution

The second danger of hypothermia, the development of postoperative bleeding tendencies, in our experience has represented more of a potential than actual hazard In the experimental animal, platelets are consistently reduced in significant numbers but we have never been able to adequately substantiate this in man In our opinion, the most important deterrent to postoperative hemorrhage is to delay closure of the wound until the patient is sufficiently rewarmed to return the blood pressure to relatively normal limits Three of our patients have had significant bleeding, an incidence of 2 1 per cent Two were successfully managed by thoracentesis One required re-exploration at which time numerous blood clots were removed but no active bleeding was encountered

From this brief discussion of the major effects of hypothermia, its potential clinical application in various cardiovascular and other surgical procedures can be appreciated If carefully administered and cognizant of the complications, with regard to their prevention and treatment, its value will far outweigh its inherent dangers This is particularly true when total body cooling is used in closed cardiac procedures or in non-cardiac operations in general

Technic

The technic employed in hypothermia is not difficult Preoperative medications are the same in type and dose as those prescribed in the normothermic individual Following induction, a constant recording esophageal or rectal thermocouple is inserted A femoral artery is catheterized and the aortic pressure measured through a strain gauge The electrocardiogram and electro-encephalogram are continuously recorded For the information of the surgeon, the pressure-pulse contour and the electrocardiogram are always visible on a monitoring oscilloscope

The actual cooling process is not started until the patient is in third stage anesthesia A refrigerating fluid is circulated through a special rubber mattress placed under the patient This mattress can surround the trunk, arms and legs similar to a sleeping bag Fluid containing tubes run to a temperature control unit and in this manner, it is possible to use the same equipment for both cooling and rewarming

It is important that shivering be prevented This is accomplished by maintaining sufficient depth of anesthesia or by administering small doses of curare when it is first noted Shivering will not only counteract the effect of the refrigerant but will actually cause the temperature to rise It also increases oxygen consumption which we believe has a detrimental effect on the hypothermia patient

We have noted that our method of cooling is slower than other reported technics To lower the temperature from 37 to 28 degrees centigrade may require from one to three hours depending on the size of the individual and the amount of left to right shunt present Most rapid cooling occurs in the non-cardiac patient or in the cardiac patient with no shunting defect Nevertheless, we prefer the slower method since it is felt to be in part responsible for our low incidence of ventricular fibrillation In this same regard, we believe it is essential that the surgical team be on hand during induction and cooling to perform any emergency procedure indicated should a serious cardiac arrhythmia develop

Cooling is discontinued when the patient's temperature is approximately two or three degrees above the desired level This amount of additional fall can be anticipated The mattress is then allowed to fall to the sides of the operating table so that as much or as little of the patient's body, necessary for the operative incision, can be exposed

In those patients requiring open cardiac procedures, hyper-ventilation is carried out for five minutes prior to circulatory occlusion This keeps the patient in a state of respiratory alkalosis and possibly lowers the incidence of ventricular fibrillation During the period of circulatory arrest,

ventilation is discontinued and the lungs are allowed to collapse With restoration of blood flow, rewarming is begun and, anesthesia wise, the patient can be carried on oxygen alone

Wound closure is delayed until the recorded blood pressure is within normal limits This is felt to be the most significant factor in preventing postoperative hemorrhage The patient is not sent to the recovery room until spontaneous respiration is adequate and the body temperature is between 33 and 34 degrees centigrade

Clinical Application of Hypothermia

During the last three years we have employed hypothermia in a variety of cardiovascular conditions These can be divided into two categories, first, cardiovascular procedures performed without circulatory occlusion and second, direct vision cardiac operations performed under complete circulatory arrest Our experience with 140 such cases would indicate that in certain instances the technic is of unquestioned value In other cases, it has virtue but is not essential Finally, in some anticipated procedures, in our opinion, it should not be employed at all (Table I)

Closed Cardiovascular Operations

One hundred twelve cardiovascular operations for a variety of conditions have been performed under hypothermia without circulatory occlusion The outcome was fatal in eight instances, an overall mortality rate of 7 1 per cent The corrected mortality rate was only 2 6 per cent since five of the patients died during the postoperative period of conditions unrelated to hypothermia Thus all deaths occurring with hypothermia for closed cardiovascular procedures were due or related to the development of serious rhythm disturbances (Table II)

Three infants with the Tetrology of Fallot had Blalock-Taussig operations performed under hypothermia of 30 to 32 degrees centigrade The

TABLE I
RESULTS IN 140 PATIENTS

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Closed Cardiovascular Operations	112	5	4 5	3	2 6	5	4 5	8	7 1
Open Heart Operations	28	2	7 1	3	10 7	1	3 5	4	14 7
TOTAL	140	7	5	6	4 3	6	4 3	12	8 5

prime consideration for its use was to improve oxygenation in these severely cyanotic patients We were impressed that the resultant decreased metabolism and oxygen utilization did improve the patient's color There was also a significant lowering of the heart rate which greatly facilitated dissection and establishment of the anastomosis Since one of our main indications for surgery was a rapidly rising hematocrit with its potential hazard of secondary thrombosis, we felt the thrombocytopenic accompanying cooling would also be of theoretical benefit Excellent results were obtained in each case Most of our patients with this malformation are doing well and are awaiting the advent of a safe extracorporeal circuit which will permit intracardiac correction of the defects For those who do require a shunting procedure, however, we believe hypothermia has definite virtue This is especially true in the infant under two years of age where surgery at normothermic levels carries a considerable risk

Two patients were operated upon with the erroneous diagnosis of val-

TABLE II
RESULTS IN 112 CLOSED CARDIOVASCULAR OPERATIONS WITHOUT CIRCULATORY OCCLUSION

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Tetrology of Fallot	3								
Infundibular Stenosis	2	2	100						
Patent Ductus Arteriosus	36	2	5 5	2	5 5			2	5 5
Coarctation of Aorta	13								
Aortic Aneurysms and Aortic Occlusive Disease	25								
Sinus Valsalva Fistula	1	1	100	1	100			1	100
Transposition of Great Vessels	1								
Portacaval Shunt	1								
Intracranial Aneurysms	30					5	16 6	5	16 6
TOTAL	112	5	4 5	3	2 6	5	4 5	8	7 1

vular pulmonary stenosis At thoracotomy the lesions were found to be infundibular Both patients were cannied at 31 degrees centigrade Closed infundibulectomies were performed and in each instance ventricular fibrillation occurred while biting out sections of the obstructing myocardium Manual cardiac compression supplemented by electrical shock restored a normal sinus rhythm and the patients made uneventful recoveries We believe this complication was caused by the stimulation of trauma on a heart whose threshold was lowered by cooling Our present policy in such cases is to perfuse the coronaries with neostigmine, occlude the inflow tracts and excise the obstructing myocardium through an open right ventriculotomy [1] The body temperature is kept at 28 degrees centigrade to allow at least eight minutes of occlusion Ultimately, however, hypothermia will undoubtedly be supplanted by the artificial circulation in this type of patient

There were 36 patients with patent ductus arteriosus operated upon under hypothermia of 30 to 32 degrees centigrade Cooling was used for two purposes, first to quiet a large, active and rapidly beating heart and second, to help sustain those patients who were considered poor surgical risks because of pulmonary hypertension The results were gratifying In the patients with severe tachycardia, the operative field was noticeably quiet and division and suture of the ductus greatly facilitated Among the poor risk patients with pulmonary hypertension, two deaths occurred Fatal fibrillation during induction developed in a three-year-old child with a large ductus, pulmonary hypertension and interatrial septal defect A second child with a large ductus and left pulmonary artery hypoplasia began fibrillating during dissection of the lesion Conversion was accomplished but an effective regular cardiac contraction could not be sustained These results have made us shy away from hypothermia in other similar patients Cooling is now limited to those who have tachycardia sufficient to cause myocardial strain or to interfere with the technical aspects of surgery

Total body cooling has been employed in 13 of the last 40 coarctations of the aorta The specific indications were first, coarctations in infants under two years of age, second, lesions associated with extensive aneurysmal dilatation of the aorta or intercostals and third, coarctations in patients with known myocardial damage In infants where it is uncertain whether the collateral circulation is sufficient to allow prolonged occlusion of the aorta without subsequent renal or spinal cord damage, hypothermia of 30 to 32 degrees centigrade provides this desired safety factor in addition to quieting a usually overactive heart It also appears to diminish the laryngeal edema occasionally seen after endotracheal intubation in infants Massive aneurysmal dilatation of the aorta and collateral intercostals is frequently observed and may be so extensive that resection of the coarcted segment is not attempted With hypothermia, dissection of these paper thin areas is aided because of the reduced head of pressure in the vessel Similarly, hemorrhage following an inadvertent laceration is less extensive and more easily controlled One patient operated upon had a coarctation

and a previous significant coronary occlusion and myocardial infarction The rationale for the use of hypothermia was to decrease the heart rate, stroke volume and cardiac output and thereby relieve the acute insult to the myocardium caused by cross clamping the aorta The 13 patients cooled for the stated reasons had the coarcted segments successfully removed with uneventful postoperative courses

There were 26 patients with aortic aneurysms, both thoracic and abdominal, and aortic occlusive disease who were cooled to the same degree as just mentioned Hypothermia proved of value in aiding the dissection, decreasing blood loss and permitting extended periods of aortic occlusion without neurologic damage The thoracic aorta could be safely obstructed for one hour and the abdominal aorta for twice that time Three of these patients developed extensive postoperative bleeding Two responded to thoracentesis, however, the third required re-operation for evacuation of blood clots With these exceptions the overall results were excellent and no other complication, which could be attributed to hypothermia, was encountered

One patient with a large sinus of valsalva fistula was unsuccessfully treated During attempted closure of the lesion, ventricular fibrillation occurred This was converted and without further attempts at fistula closure, the patient was sent to the recovery ward Six hours later the arrhythmia recurred and resulted in death This complication was believed due to operative interference with the coronary circulation rather than the use of hypothermia However, further knowledge of this lesion as regards its pathologic anatomy would indicate that hypothermia will not be adequate to permit its successful obliteration The necessary surgical procedure would appear to depend upon the safe application of an extracorporeal circuit

One patient with a transposition of the great vessels was operated upon under hypothermia of 30 degrees centigrade The basis for its application was the same as that already presented for the cyanotic tetrology of Fallot The infant was severely ill, cyanotic and had a hematocrit of 84 The procedure described by Baffes,[2] in which the inferior vena cava is transposed to drain into the left atrium and the right pulmonary vein is anastomosed to the right atrium, was employed The result was most gratifying There was marked lessening of the cyanosis and the hematocrit at the time of discharge had fallen to 57 A venous angiocardiogram through the femoral vein demonstrated adequate function of the operative repositioning of the cava and pulmonary vein Until more complete and safe corrective operations are available, the Baffes procedure performed under hypothermia seems to greatly improve these unfortunate individuals

Total body cooling also appeared to have application in the cirrhotic patient requiring a portacaval shunt It was believed indicated when liver function was so depressed that surgery at normothermic levels was contraindicated The cooling not only decreased the amount of anesthetic agent administered but, by lowering liver metabolism, lessened the possibility of postoperative hepatic failure

One patient with chronic jaundice, recurrent hematemesis and liver failure had a direct end-to-side portacaval shunt established under hypothermia of 30 degrees centigrade This individual would most certainly have gone into hepatic coma under normal operative conditions Hypothermia provided the needed safety factor to carry the patient successfully through the significant anesthetic and operative insult imposed on an already severely damaged liver

This technic has offered hope to additional patients who formerly were denied the possible advantages of the shunt operation With further application it may even lower the postoperative morbidity in those patients with less severe hepatic changes

The remaining 30 patients in the category of cardiovascular lesions repaired under hypothermia without circulatory occlusion had various types of intracranial aneurysms and vascular malformations The application of total body cooling in these individuals was predicated upon its effect in decreasing cerebral edema both during and after operation and in allowing short periods of cerebrovascular occlusion Clinically, it has proved efficient in the former However, in the latter regard, periods of six to eight minutes of occlusion are insufficient to adequately perform the surgery required New technics of hypothermia, at present being studied, should meet these expanded requirements

TABLE III
RESULTS IN 28 OPEN HEART OPERATIONS WITH COMPLETE CIRCULATORY OCCLUSION

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Pulmonary Valvular Stenosis	11								
Interatrial Septal Defect	16	1	6 2	2	12 4	1	6 2	3	18 7
Secundum	12								
Primum	2					1	50	1	50
Atrioventricularis Communis	2	1	50	2	100			2	100
Pulmonary Aortic Window	1	1	100	1	100			1	100
TOTAL	28	2	7 1	3	10 7	1	3 5	4	14 2

Open Cardiac Operations

The second major category of patients undergoing hypothermia were those on whom open cardiac operations were performed during complete circulatory interruption These included pulmonary valvular stenosis, pulmonary aortic window and interatrial septal defect The obvious indication for body cooling was to permit temporary cessation of blood flow and assure an accurate and complete repair of the defect by direct vision in an open and relatively dry heart There were 28 patients treated with four deaths (14 2 per cent) Ventricular fibrillation developed in two patients (7 1 per cent) Both succumbed and are included in the deaths just mentioned The arrhythmia had its onset during induction in one patient and during cardiac manipulation in the other (Table III) In contradistinction to the group of patients in whom the circulation was not occluded, where all deaths were related to arrhythmia, only half of the deaths in the open heart group could be attributed to this cause

We believe the direct open attack on the stenotic pulmonary valve is superior to the closed valvulotomy and our last 11 patients were handled in this manner Initially, hypothermia of 28 degrees centigrade was used but experience has shown that this depth is not required We have steadily decreased the amount of cooling to our present figure of 32 to 33 degrees centigrade Since the open portion of the operation can be performed in less than three minutes, it is assumed the procedure could be safely done in a normothermic individual Nevertheless, we have been reticent to relinquish the last several degrees of cooling because of the protection they provide should a situation be encountered that would take over three minutes to resolve

There are several points of interest regarding surgical technic To obtain a dry operative field, it is not necessary to occlude both inflow and outflow tracts Obstruction of the cavae is sufficient Air emboli in the unobstructed pulmonary artery has not presented a problem This technic has been of particular benefit in the small infant where cross clamping the outflow tracts markedly constricts an already tiny operative field It is important that the pulmonary artery be opened as close to the valve as possible and the commissures be incised to the annulus Finally, a finger or large hemostat should be passed into the ventricle to be certain no associated infundibular stenosis is present

There has been no morbidity or mortality connected with this procedure The results have been excellent and postoperative catheterization has revealed right ventricular pressures to be normal or nearer normal than those obtained following closed valvulotomy

One patient with a massive pulmonary aortic window was operated upon under hypothermia of 28 degrees centigrade During division and suture of the lesion, ventricular fibrillation occurred The total period of vascular stasis was 12 minutes Manual cardiac compression was carried out for almost six hours and only discontinued when the heart failed to show evidence of electrical activity This patient presented a lesion too extensive to be properly managed under hypothermia An adequate recon-

struction of the great vessels could not be completed within the eight minute safe period A small defect well out on the outflow tract could undoubtedly be successfully managed However, since it is almost impossible to determine preoperatively the size of a window, especially with regard to its proximal extent and possible valve involvement, it would seem that repair should be attempted only if an extracorporeal circulation is available

The final group of patients to be discussed are those with interatrial septal defect Though many operative procedures have been devised to repair this lesion, our experience with the closed heart procedures, with the exception of atrioseptopexy, has been discouraging Very small secondary defects are often impossible to locate with the blindly palpating finger and are therefore incompletely closed or missed entirely Several external repairs performed on a greatly distended and wildly beating heart have torn through during surgery or in the early postoperative period For these reasons, plus the belief that there is no substitute for direct vision, we have relied on hypothermia and an open heart to repair the last 16 defects

The patient is cooled to approximately 28 to 30 degrees centigrade and the right atrium digitally explored Both inflow and outflow occlusion are employed Three things were particularly impressive at cardiotomy First was the high incidence of secondary defects which could not be palpated Second was the firm tissue which constituted the rim of the defect and gave substance to the suture closure Third was the facility with which transposed veins could be repositioned into the left atrium Fear of air embolism was considerable However, this complication was usually avoided by allowing the left heart to fill by spillover from the right before the final suture in the defect was tied Significant air was trapped in the coronaries in one patient Approximately one hour of intermittent cardiac compression was required to establish an effective normal rhythm The patient was comatose for five days but has subsequently made a complete recovery

Three deaths occurred in the series giving an overall mortality rate of 18 6 per cent However, this figure becomes less significant when one considers the type lesions involved There were 12 patients with septum secundum defects, all successfully repaired without mortality In two instances a septum primum defect was encountered In one patient, the extent of the defect and the surrounding relationships were misinterpreted during suture The condition was corrected but the delay was sufficient to produce irreversible myocardial damage The second patient did well except for a temporary partial heart block postoperatively Therefore the mortality rate with primum defects was 50 per cent Surgery was also attempted on two patients with atrioventricularis communis lesions One died of cardiac arrhythmia during induction In the second patient, the defect including the deformed mitral valve was repaired but on restoring the circulation an effective cardiac contraction could never be established The mortality rate was 100 per cent From these figures it would appear

that hypothermia can be considered adequate for the successful correction of all secundum defects and possibly primum lesions Repair of the common atrioventricular canal with its associated valvular deformities will require additional time which can best be obtained by employing a pump-oxygenator system

SUMMARY

A study was made of 140 patients who were operated upon under hypothermia for cardiovascular lesions One hundred twelve had the operations performed without occlusion of the circulatory system Of eight operative deaths, only three could be directly related to the body cooling

Open cardiac procedures were performed in 28 instances with complete circulatory arrest for periods varying from two to 10 minutes Of four operative deaths three were associated with hypothermia

RESUMEN

Se estudiaron 140 enfermos operados bajo hipotermia por lesiones cardiovasculares 112 sufrieron sus operaciones sin oclusión del sistema circulatorio De las ocho muertes operatorias, sólo tres podrían tener relación con el enfriamiento directamente

Se realizaron 28 operaciones a corazón abierto con paro circulatorio variando de 2 a 10 minutos De cuatro muertes operatorias, tres estuvieron asociadas a la hipotermia

RESUME

L'auteur rapporte une étude de 140 malades opérés sous hypothermie pour des lesions cardiovasculaires 112 subirent des interventions sans arrêt du système circulatoire Sur les 8 morts opératoires, trois seulement peuvent être liées directement au refroidissement

Des interventions à coeur ouvert furent pratiquées dans 28 cas avec arrêt complet de la circulation pendant des laps de temps allant de 2 à 10 minutes Sur quatre morts opératoires, trois furent imputables à l'hypothermie

ZUSAMMENFASSUNG

Es wurden 140 Patienten untersucht, die wegen cardiovascularer Veränderungen unter Hypothermie operiert wurden Bei 112 wurden die Eingriffe vorgenommen ohne Verschluss des Kreislaufes Von 8 operativen Todesfallen konnten nur 3 in direkte Beziehung gesetzt werden zu der Unterkuhlung des Korpers

Eingriffe am offenen Herzen wurden in 28 Fallen vorgenommen mit vollstandigem Kreislaufstillstand fur Zeitabschnitte, die zwischen 2 und 10 Minuten lagen Von 4 operativen Todesfallen standen 3 in Verbindung mit der Hypothermie

REFERENCES

1 Swan, H, Virtue, R W, Blount, S G, Jr and Kircher, L T, Jr "Hypothermia in Surgery, Analysis of 100 Clinical Cases," *Ann Surg*, 142 382, 1955

2 Baffes, T G "A New Method for Surgical Correction of Transposition of the Aorta and Pulmonary Artery," *Surg, Gynec and Obst*, 102 227, 1956

Atrial Septal Defect: An Evaluation of Surgical Closure*

STEPHEN A KIEFFER, B S**
Minneapolis, Minnesota

Successful surgical closure of an atrial septal defect was first performed by Bailey[1] in January, 1952, employing the method he terms atrio-septo pexy Cohn[2] in 1947 had reported results of the first experimental closure of defects in the atrial septum, and only a year later Murray[3] reported the first attempt at repair in a 12-year-old child by approximating the anterior and posterior atrial walls in the region of the septum While early-post-operative evaluation of this case was optimistic, cardiac catheterization 14 months post-operatively by Keith and Forsyth[4] demonstrated a substantial left-to-right shunt and significant pulmonary hypertension with one episode of cardiac failure during this period

Within two years of Bailey's first successful closure by atrio-septo-pexy, three other techniques of successful surgical correction of this relatively common congenital cardiac defect were reported in the literature Sondergaard[5] in Denmark and Bjork and Crafoord[6] in Sweden introduced the method of circumclusion Gross[7] applied a prosthesis of rubber or woven nylon to the right atrium and closed the defect through this "atrial well" Lewis[8] and Swan[9], employing hypothermia, were the first to work in an open heart under direct vision, although later Lillehei[10 11] and Cooley and Kirklin[12] initiated the use of an extracorporeal circulation

To evaluate the results of surgical closure of the various types of atrial septal defect by the several techniques listed above and to attempt to define present indications and contraindications for closure are the purposes of this communication

Methods and Material

The literature for the years 1954 through 1956 inclusive was reviewed Each series of cases of atrial septal defect submitted to surgery and reported in the literature was tabulated Criteria for appraising results of surgery were established prior to undertaking the study, and the outcome of every case tabulated from the literature was critically evaluated according to these standards, which included

Good — Complete closure of defect proved by post-operative cardiac catheterization, and/or uncomplicated clinical post-operative course with regression or complete loss of symptoms General clinical impression that defect was completely closed

Fair — Some residual interatrial shunting of blood proved by post-operative cardiac catheterization, and/or clinical impression that a small residual shunt existed following surgery although there was

*Third Prize, 1957 Essay Contest, American College of Chest Physicians
**Department of Pediatrics, University of Minnesota Medical School

definite clinical evidence of benefit from operation

Poor — Large residual interatrial shunt proved by post-operative cardiac catheterization, and/or lack of significant improvement on postoperative clinical evaluation

On the basis of embryological and post-mortem findings, atrial septal defects historically have been separated into two groups, the ostium primum defects and the ostium secundum defects This division has been made purely on location, the primum type being lower in the septum and adjacent to the atrioventricular valves and ventricular septum, while the secundum defect is commonly higher in the atrial septum in the region of the foramen ovale or posterior to this landmark

Recent surgical and pathological investigations[13, 14] have brought to light the fact that the ostium primum defect is nearly always associated with a cleft mitral valve As Figure 1 demonstrates, this lesion differs only slightly from the complete persistent atrio-ventricularis communis, in which the low atrial septal defect is associated with a high ventricular septal defect and a five-cusped common atrio-ventricular valve

Brandenburg and DuShane[15] estimate that 10 to 15 per cent of all cases of atrial septal defect are of the atrio-ventricularis communis variety While the mean age at death in the complete form is only 10 months, patients with partial type commonly reach adult life, many with only the mildest of symptoms Though the mitral valve is incompetent anatomically, a significant proportion of patients give no hemodynamic evidence of mitral regurgitation

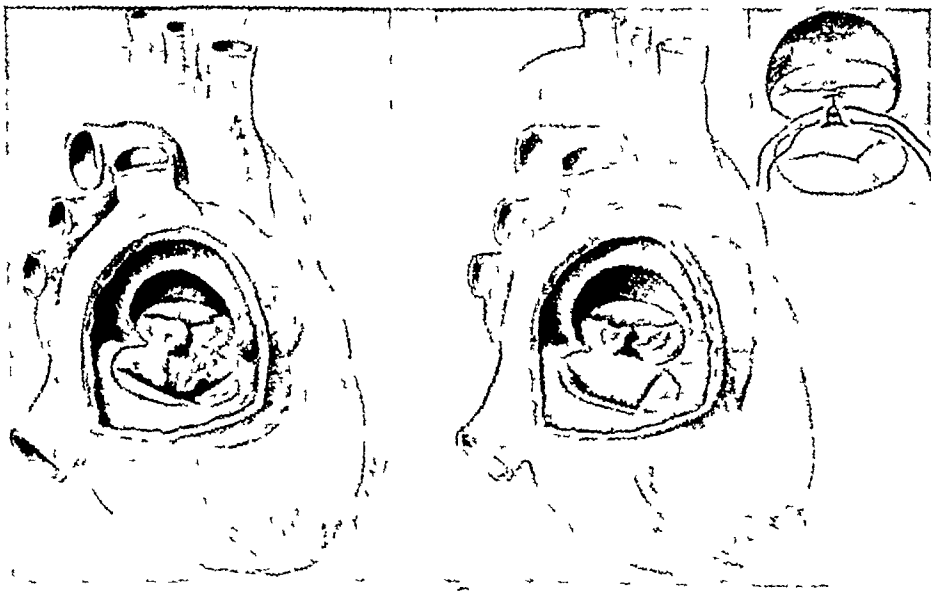


FIGURE 1 Persistent atrio-ventricularis communis A Complete form The defect in the atrial and ventricular septa is visualized Both atrio-ventricular valves are cleft, the leaflets in reality forming a five-cusped common atrio-ventricular valve A bare area of muscular ventricular septum is seen forming the inferior margin of the defect B Partial form Only the mitral valve is cleft The insert demonstrates the technique for repair of the valvular deformity (From Cooley, J C, Kirklin, J W and Harshberger, H C "The Surgical Treatment of Persistent Common Atrioventricular Canal," *Surgery*, 41 147, 1957)

TABLE I

SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY ATRIO-SEPTO-PEXY

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Evaluation	Cases	Deaths	Good	Fair	Poor	Unevaluated
1 Longmire et al[21]							15	0	11	0	2	2						
2 Husfeldt[22]	2	0	0	1	1	0	4	0	1	0	0	3	6	0	2	0	1	3
3 Kay et al[23]													15	1	0	0	0	14
4 Dahlback et al[24]	2	1	0	0	1	0	7	0	1	2	1	0						
5 Moeys[25]	2	1	0	1	0	0												
6 Bailey et al[26]	16	11	4	1	0	0	57	5	27	2	0	23						
7 Schumacker[20]							1	0	1	0	0	0						
8 Brando et al[27]													2	1	1	0	0	0
TOTAL	21	12 (57.1 %)	4	3	2	0	84	5 (6.0 %)	44	4	3	28	23	2 (8.7 %)	3	0	1	17

The ostium secundum defect arises from abnormal resorption of the septum primum There results an incompetent valve of the foramen ovale, or, if resorption is too great and growth of the septum secundum is defective, a large defect is produced [16] This type of communication usually is located centrally or posteriorly in the atrial septum and is separated from the atrio-ventricular ridge by a rim of septal tissue [17] It is compatible with a longer life span than either form of persistent atrioventricularis communis Roesler[18] reported a mean age at death in 62 cases of 34 years, while Abbott's[19] mean for 55 cases was 31 years

Present diagnostic techniques cannot distinguish these two lesions before surgery,[14] and results of both forms of persistent atrio-ventricularis communis have therefore been included in this study

Wherever the literature indicated the type of defect being corrected, this was noted Often, however, these reports did not give this information, thus requiring three categories for tabulating results of surgical therapy persistent atrio-ventricularis communis (partial and complete forms), ostium secundum defect, and undifferentiated atrial septal defect

With slight exception, this survey has been limited to cases of atrial septal defect and persistent atrio-ventricularis communis uncomplicated by further cardiac pathology The only companion anomaly reported with a significant degree of frequency in the literature was a partial anomalous pulmonary venous return, which was noted in 28 of 281 cases of ostium secundum defect submitted to surgery Cases with such infrequent companion lesions as pulmonary stenosis, ventricular septal defect, or total anomalous pulmonary venous return were not included in this surgery

Techniques and Results of Surgical Closure

The four techniques described in the introduction are the methods of closure which have been widely adopted and reported in the literature Atrio-septo-pexy, circumclusion, and the atrial well technique are all considered "closed" methods of repair in contrast to "open" methods where the operator is allowed to visualize the defect Each technique will be discussed under individual heading

Atrio-septo-pexy

This earliest successful technique of repair was not devised with the primary surgical objective of direct anatomic closure of the defect Rather, Bailey[1] states, the goal was to separate "the two venous systems to the respective atrio-ventricular valves" The redundant anterolateral wall of the dilated right atrium is approximated to the posterior remnant of the septum or to the posterior atrial wall, thus creating a new intracardiac passageway for the flow of vena caval blood Then, the lateral atrial wall is invaginated against the septum and sutures are placed in the margin of the defect as demonstrated in Figure 2 Accuracy in this procedure is aided by the insertion of the ungloved index finger into the right atrium through an incision in the auricular appendage, the finger then guiding placement of sutures in the septal rim Schumacker[20] modi-

fied this technique by invaginating a woven nylon pocket sutured to the lateral atrial walls instead of using actual atrial tissue

Results of atrio-septo-pexy are tabulated and evaluated in Table I Eight medical centers have reported experience with this method Bailey feels it is particularly well adapted to treatment of associated mitral stenosis or partial anomalous pulmonary venous return The presence of the index finger within the heart enables the surgeon to perform a digital commissurotomy of the stenosed mitral valve through the septal defect prior to closure By approximating the lateral wall only to the anterior margin of the defect, a third chamber is created, and the anomalous right pulmonary veins drain directly into the left atrium through the unclosed defect

Even a cursory glance at Table I will make the reader aware of the wide gap between the results of surgery in persistent atrio-ventricularis communis and ostium secundum atrial septal defect The lack of an inferior remnant of atrial septum in the former lesion necessitates placing

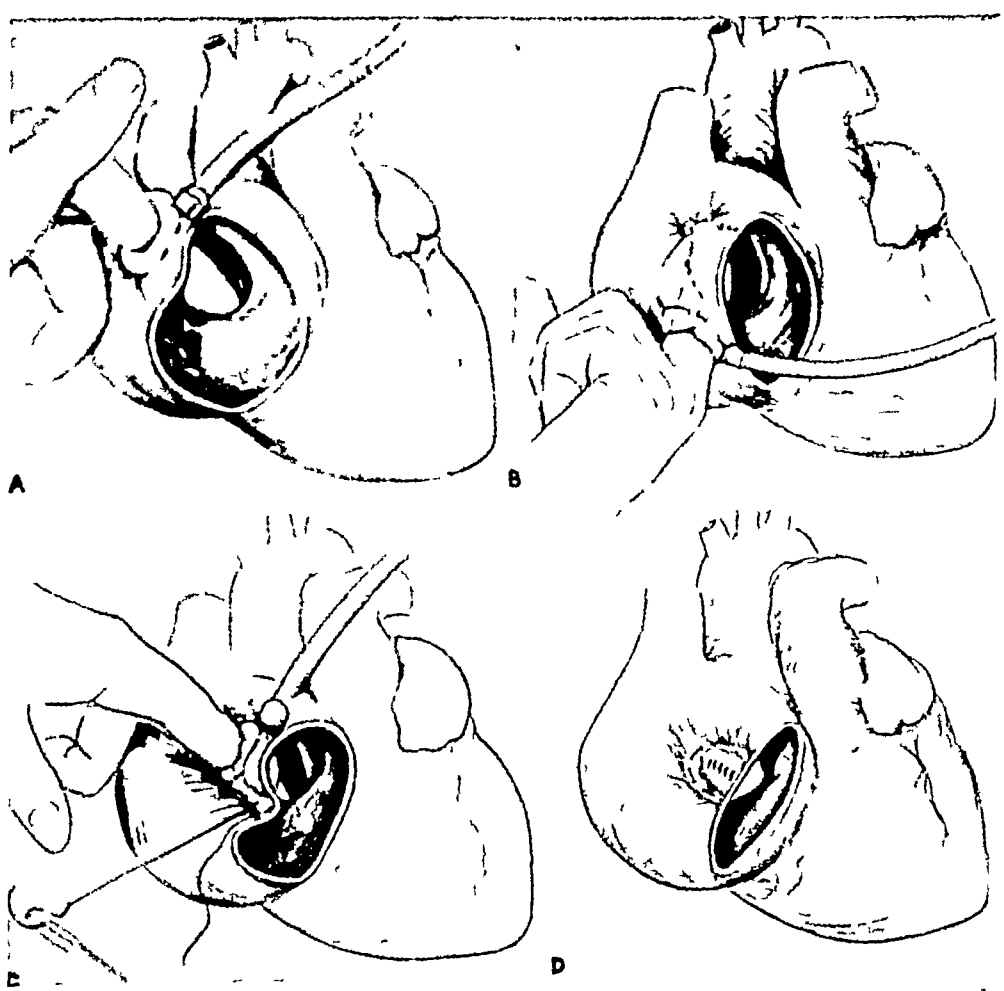


FIGURE 2 Closure of ostium secundum defect by atrio-septo-pexy A Digital exploration via right auricular appendage B Placement of first suture C Approximation of invaginated right atrial wall to periphery of septal defect D Completion of atrio-septo-pexy (From Bailey, C P, in "Henry Ford Hospital International Symposium on Cardiovascular Surgery," Philadelphia, W B Saunders Company, 1955, p 350)

sutures in the upper margin of the ventricular septum This has frequently caused interruption of the common conduction bundle of His and consequent atrio-ventricular dissociation Bailey attempted to avoid the atrio ventricular node and bundle by omitting placement of sutures in the ventral portion of the membranous septum This measure was not successful, however, and this group has abandoned the use of atrio-septo-pexy for closure of atrio-ventricularis communis defects [28] Others have met with similar results

Of 84 ostium secundum cases reported, only five succumbed, a mortality of 6 0 per cent Forty-four of 51 survivors evaluated post-operatively give a clinical impression of complete closure of the defect and consequent regression and loss of symptoms Bailey repotrs complete closure in 14 of 16 cases catheterized post-operatively with the remaining two persons demonstrating small residual defects which have not prevented marked improvement and benefit from operation Longmire[21] has recently reported surgical closure by atrio-septo-pexy on 15 cases of ostium secundum defect without mortality Employing three of the accepted techniques for closure, this group has operated on 34 patients They state a preference for atrio-septo-pexy over other "closed" methods or repair, terming this the easiest and least hazardous of "closed" techniques

The 23 cases listed as undifferentiated as to type of defect in Table I included only two deaths, inferring that nearly all were of the ostium secundum variety

Circumclusion

Eleven medical centers, five of them in Europe, have employed circumclusion or a modification of this technique to close atrial septal defects

It was Sondergaard[5] who originally conceived the procedure of dissecting a plane of cleavage between the two atria on their posterior aspect His original work on dogs had demonstrated the presence of a fatty layer separating the atria posteriorly and continuous with the muscular interatrial septum, and he was able to dissect a considerable distance into this fatty septum between the venae cavae and the right pulmonary veins Bjork and Crafoord[6] introduced the use of the intracardiac finger inserted through the right auricular appendage to aid in passing the circumcluding needle with suture from the upper limit of the cleavage near the base of the aorta through the anterior and inferior margins of the septal remnant and out posteriorly behind the vena cavae This group first utilized circumclusion on a human patient Sondergaard[29] later replaced the needle with a blunt flexible probe which is passed around the margin of the defect in the same path, as Figure 3 demonstrates A suture is tied to the tip of the probe, drawn back through the intraseptal tunnel created by the probe, and then pulled tight thus circumcluding the defect The suture is tied in the interatrial cleavage plane over a section of plastic, fascia, or muscle Not only does dissection of this plane aid in accurate placement of the circumcluding suture, but also it prevents obstruction of the superior vena cava or the pulmonary veins when the suture is tied down

TABLE II
SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY CIRCUMCLUSION
(And Modifications of This Technique)

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
1 Bosher[30]							12	0	7	0	0	5						
2 McNamara-Cooley[31]	3	0	3	0	0	0	1	0	1	0	0	0						
3 Edwards et al[32]	4	0	0	4	0	0	7	2	3	2	0	0						
4 Gerbode[33]	1	0	0	1	0	0	4	2	2	0	0	0						
5 Senning[34]							3	0	0	0	0	3						
6 Sondergaard[35]	2	0	0	0	2	0	8	0	8	0	0	0						
7 Husfeldt[37]													21	5	0	0	9	7
8 Walker et al[36]							2	0	1	1	0	0						
9 Southworth-Dabbs[7]	1	0	0	1	0	0												
10 Bjork-Crafoord[38]													12	2	1	0	0	9
11 Lam[39]	4	2	0	0	2	0	12	0	0	0	0	12						
TOTAL	15	2 (13.3 %)	3	6	4	0	49	4 (8.2 %)	22	3	0	20	33	7 (21.2 %)	1	0	9	16

The techniques of Sondergaard and Bjork and Crafoord have been modified to a considerable extent by other workers, but all save one retain the dissection of an interatrial cleavage plane as essential to their methods Only Edwards[12] does not dissect out this groove He passes the circumcluding suture directly through the fatty septum McNamara and Cooley[71] and Bosher[30] reinforce the circumcluding suture by passing interrupted sutures around it in the anterior and inferior rim of the defect, then drawing those sutures back through the cleavage plane and tying them over polyvinyl sponge Lam,[39] Gerbode,[33] and Senning[34] do not utilize the circumcluding suture, but rather employ various methods of approximating the anterior rim of the defect to the posterior atrial wall in the plane of the cleavage

Among the advantages of circumclusion, Sondergaard[40] includes the unaltered shape and function of the atria and the lack of exposed sutures or other foreign bodies within the heart In atrio-ventricularis communis lesions, where the lack of an inferior atrial septal margin requires that the probe or needle be passed through the upper ventricular septum, the fact that it slides parallel to the course of the bundle of His reduces atrio-ventricular conduction difficulties due to method of surgery

The results of surgical closure of atrial septal defects by circumclusion and related techniques are tabulated in Table II Despite the lack

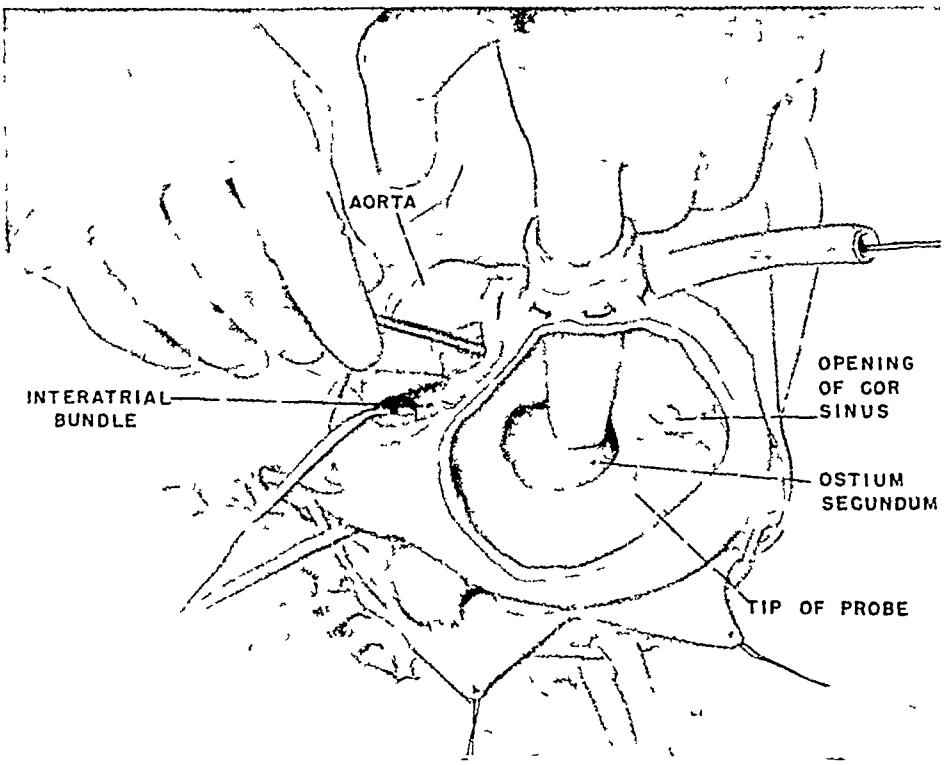


FIGURE 3 Closure of ostium secundum defect by circumclusion The probe is inserted into the atrial septum at the root of the aorta and guided around the septal margin emerging behind the inferior vena cava It is then drawn back, carrying with it the circumcluding suture (From Bosher, L H, Jr "Repair of Interatrial Septal Defects by a Modified Sondergaard Technique (Circumclusion)," *Surgery*, 41 129, 1957)

TABLE III

SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT EMPLOYING AN ATRIAL WELL

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
1 Bernatz-[46] Kirklin et al[47]	2	0	1	1	0	0	31	1	26	3	1	0	27	2	9	0	0	25
2 Longmire et al[21]							15	2	9	0	2	2						
3 Walker[30]							3	0	2	0	1	0						
4 Muller et al[49]	1	0	0	0	0	0												
TOTAL	3	0 (0 0 %)	1	1	1	0	49	3 (6 1 %)	37	3	4	2	27	2 (7 4 %)	0	0	0	25

of conduction difficulties, only three of 13 survivors with persistent atrioventricularis communis were considered to have complete repair of the deformity on post-operative clinical evaluation The remaining 10 persons derived little or no benefit from operation

Mortality in the ostium secundum group was only 8 2 per cent with 22 of 25 survivors demonstrating complete closure on post-operative clinical evaluation

In 1954, Husfeldt,[41] employing the technique of Sondergaard, reported complete closures of the defect in all survivors in a group of both atrioventricularis communis and ostium secundum cases In a communication one year later,[22] however, he reported the shunt reestablished in every case on clinical evaluation eight to 21 months after operation One of these patients was again submitted to surgery, the circumcluding suture was found to have transected the septal tissue, allowing the defect to reopen No other group has reported this complication

Atrial Well Technique

The atrial well technique may be regarded as a semi-open method of closure of atrial septal defects While atrio-septo-pexy and circumclusion allow only one digit to be inserted into the right atrium, this procedure permits the passage of several fingers into the atrial chamber [42] It has been employed at five medical centers in the United States Results are tabulated and evaluated in Table III

The technique as introduced by Gross involves a wide right-sided thoracotomy with the patient in the left lateral position A clamp is placed on a portion of the lateral wall of the right atrium and a single long incision is made through this pocket of tissue After a rubber or nylon "well" is sutured to the margins of the incision, the clamp is released and the blood rises slowly into the well (Figure 4) The fingers are passed into the atrial chamber through this pool of blood, allowing, through tactile direction, closure of the septal defect by direct suture or by the onlay of polyethylene sheet shaped to cover the defect Kirkland,[43, 44] who has operated on the largest series of cases with this method, has modified Gross's technique by administering 300 to 500 cc of blood to the patient before entering the heart to prevent any effects of sudden blood loss This group systematically inserts a section of polyvinyl sponge through the well and anchors this to the left side of the septal remnant The tendency of the blood to flow from left to right across the septum further abuts the sponge against the remnant, aiding in complete closure With time the sponge is first covered by a layer of fibrin and later converted to a smooth glistening membrane through endotheliazation [45] Heparin is dripped slowly into the well to prevent clotting of the blood, an injection of protamine after the atrial incision is closed neutralizing the anticoagulant

In 1955, Watkins and Gross[48] reported the results of surgical repair in 43 cases of atrial septal defect and noted that external suture methods of closure and not the atrial well technique had been employed in the last 30 cases Kirklin,[46 47] however, continued to use this method through

early 1956, attaining a total of 60 cases In 49 cases of ostium secundum defect reported by three groups, there were only three deaths, a mortality of 6 1 per cent Seven of the 46 survivors have residual shunts of significant degree on post-operative clinical evaluation Only three persons with persistent atrio-ventricularis communis lesions have been submitted to this technique of repair While there was no mortality, two of the three received little or no benefit from surgery

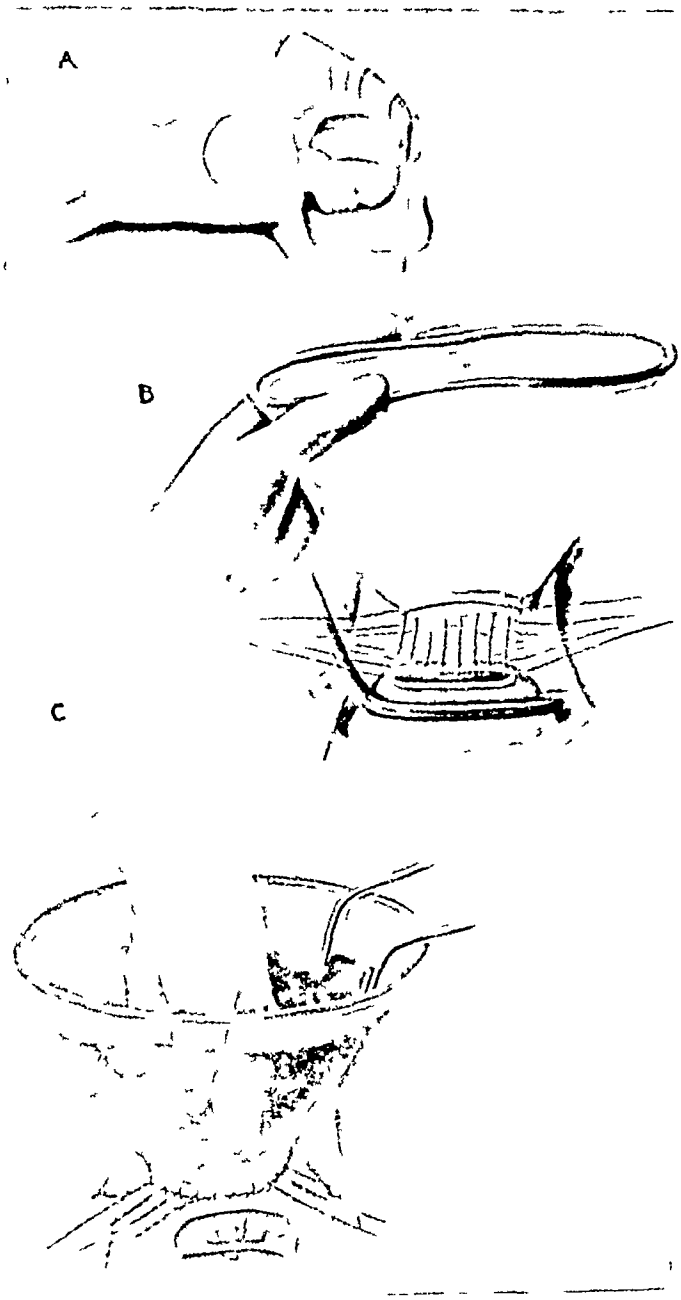


FIGURE 4 The atrial well technique A Position of chest wound B Attaching a rubber "well" to the wall of the right atrium C With the well in place, the atrial wall opened widely at its base, the fingers are inserted through the pool of blood into the atrial chamber, and the septal defect may be closed (From Gross, R E and Watkins, E, Jr "Surgical Closure of Atrial Septal Defects," *A M A Arch Surg*, 67 670, 1953)

Direct Vision Techniques

Within a year of the introduction of atrio septo-pexy, Lewis[8] had achieved successful closure of an atrial septal defect in an open heart under hypothermia Experimental research with temporary occlusion of the flow into the heart in order to obtain an open dry field had been conducted as long ago as 1907 by Haeker [50] Application of this procedure to surgery on the human heart had been limited by the rapid ischemic effects on the tissues, especially the brain and central nervous system By reducing tissue oxygen consumption, however, low body temperature has permitted occlusion of the venae cavae for short periods of time and opened the way for direct vision intracardiac surgery

Several techniques for cooling the body have been utilized in closure of atrial septal defects Kimoto[71] cannulates the common carotid artery, drawing the blood through a heat exchange coil submerged in a refrigerant and thus cooling the brain Nine cases of atrial septal defect, three described specifically as ostium secundum and six undifferentiated as to type, have been submitted to surgery There has been no operative mortality, and all nine patients demonstrate complete closure on clinical post-operative evaluation

Lewis,[52] Swan,[53] Salyer,[55] and Longmire[21] have employed surface cooling techniques to induce hypothermia The anesthetized patient is immersed in ice water until his body temperature falls to the desired level for surgery Lewis has worked within a range of 24 5 to 29 5 degrees Centigrade, while Swan and Longmire and Salyer prefer somewhat higher temperatures Even at 31 degrees Centigrade, tissue oxygen consumption is only 55 per cent of normal [54] All direct vision methods require a bilateral thoracotomy, transecting the sternum Occlusion of the venae cavae is limited to a period of less than eight minutes The right atrium is incised widely and the defect is repaired, employing continuous suture approximation of the margins of small defects and polyethylene or polyvinyl sections to close larger openings The limited period of inflow occlusion prevents suture approximation of the two leaflets of the cleft mitral valve in persistent atrio-ventricularis communis After closure of thoracotomy incision, the patient is rapidly rewarmed to near normal body temperature

These five groups have used hypothermia for direct-vision closure of 93 cases of ostium secundum atrial septal defect (Table IV) Although there have been 11 deaths due to operation, 50 of 53 patients evaluated post-operatively have demonstrated complete abolition of the shunt, and there have been no poor results in this group The outcome in 10 cases of persistent atrio-ventricularis communis has not been nearly as encouraging, there have been only four survivors and only one of these appears to have had complete repair of his deformity Both Lewis and Swan report a tendency for patients in the hypothermic state to go into ventricular fibrillation, and this is cited as the cause for several of the operative deaths Induction of respiratory alkalosis by administration of carbon dioxide or injection of prostigmine into the sino-atrial node

TABLE IV
SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY DIRECT VISION TECHNIQUES

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
					Post-Operative Evaluation						Post-Operative Evaluation					Post-Operative Evaluation		
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
Hypothermia																		
1 Swan-Blount[17]	4	2	1	0	1	0	45	7	26	1	0	11						
2 Salyer et al[55]							12	1	10	1	9	0						
3 Longmire et al[21]							4	0	0	0	0	4	6	0	6	0	0	0
4 Kimoto et al[51]							3	0	3	0	0	0						
5 Lewis et al[57]	6	4	0	2	0	0	29	3	11	1	0	14	6	0	6	0	0	0
Subtotal	10	6 (60 0 %)	1	2	1	0	93	11 (11 8 %)	50	3	0	29		(0 0 %)				
6 Lillehei et al[10]	4	3 (75 0 %)	1	0	0	0												
Pump-Oxygenator																		
7 Dennis[59]																		
8 Cooley-Kirklin[12]	9	2	7	0	0	0							1	0	1	0	0	0
9 Lillehei[57]	11	7	4	0	0	0	6	0	6	0	0	0						
Subtotal	20	9 (45 0 %)	11	0	0	0	6	0 (0 0 %)	6	0	0	0	1	0 (0 0 %)	1	0	0	0
TOTAL	34	18 (52 9 %)	13	2	1	0	99	11	56	3	0	29	7	0 (0 0 %)	7	0	0	0

are proposed as means of preventing this complication, but neither procedure has yet been clearly substantiated by clinical trial. Swan[58] also reports transient peripheral neuropathies in twelve patients following

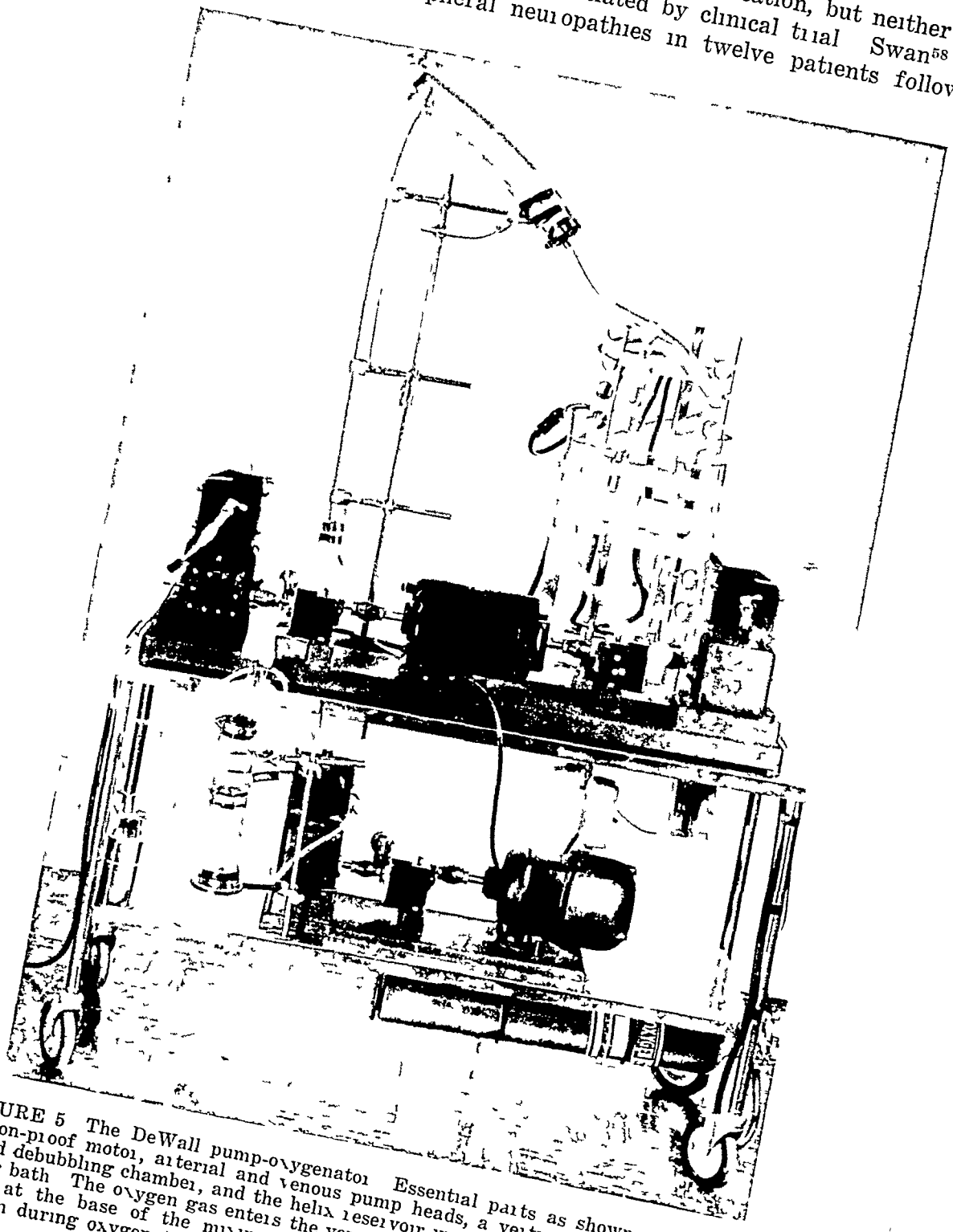


FIGURE 5 The DeWall pump-oxygenator. Essential parts as shown include an explosion-proof motor, arterial and venous pump heads, a vertical mixing tube, and inclined debubbling chamber, and the helix reservoir immersed in a constant temperature water bath. The oxygen gas enters the venous blood directly through a nylon diffusion plate at the base of the mixing tube. Venous carbon dioxide escapes with excess oxygen during oxygenation.

intracardiac surgery under hypothermia and warns of blood coagulation abnormalities below 28 5 degrees Centigrade

Various experimental attempts have been made to substitute an extracorporeal circulation for the patient's heart and lungs, relieving these organs of the obligation to oxygenate the blood and circulate it to the tissues and allowing the surgeon to work in a bloodless heart for longer periods than hypothermia permits One of the most interesting of these methods to be given clinical trial was controlled cross circulation Lillehei and Varco,[59] utilizing a human donor to oxygenate the patient's blood, closed the septal defects and repaired the valvular deformity in three cases of persistent atrioventricularis communis Unoxygenated blood from the patient's venae cavae was drawn by catheters into the donor's great saphenous vein, and oxygenated blood was returned from the donor's superficial femoral artery to the patient's subclavian artery Auxiliary pumps and an arterial blood reservoir were interposed between the two circulations The one survivor of this procedure demonstrated complete closure of the defect and abolition of valvular regurgitation on post-operative cardiac catheterization [10]

At present, the most advanced refinement of the extracorporeal circulation is the mechanical pump-oxygenator as originally proposed by Gibbon in the mid-thirties [60] The venae cavae and the aorta are cannulated and occluded and the catheters are connected to the pump-oxygenator During the past two years, three different pump-oxygenators have been employed in the closure of atrial septal defects Dennis[56] and Kirklin[61] use apparatus in which a film of blood less than a millimeter in thickness flows over fine mesh screen within an oxygenating chamber Kirklin employs parallel rectangular vertical screens according to the scheme of Gibbon, while Dennis uses four rotating screen discs Lillehei[11] utilizes a vertical plastic oxygenator (Figure 5), the blood mixing with large bubbles of pure oxygen This group has shown that the patient can and does survive surgery without ill effect while the pump oxygenator circulates less than one half the usual cardiac output of a normal human of similar size

With the pump-oxygenator there is no limit to the period of occlusion of the vessels leading to and from the heart [56] This allows location and repair of valvular deformities in cases of persistent atrio-ventricularis communis By avoiding placement of stitches in the posterior half of the ventricular septum and at the posterior junction of the atrial septum and the atrio-ventricular valves, interference with the common conduction bundle may be averted,[12] and the septal defects may be closed with fewer complications The valvular deformity is repaired (Figure 1*b*) and the defect is closed by continuous suture approximation of its margins or by anchoring a polyvinyl section to the septum with interrupted sutures Results have been equivocal in the first 20 cases While mortality has exceeded 40 per cent, the eleven survivors all demonstrate complete repair of this complex anomaly on post-operative clinical evaluation

There has been no mortality in six cases of ostium secundum atrial

septal defect closure with the pump-oxygenator, all six patients demonstrate complete closure post-operatively [57]

Ostium Secundum Atrial Septal Defect

All of the techniques described above for repair of ostium secundum atrial septal defects have been employed with success (Table V) Only five years after the first successful closure, the operative mortality in any of the accepted procedures approximates one case in 10 or better

To give the seal of approval to one of these techniques to the exclusion of the other three would be a mistake Each has its own advantages and disadvantages as enumerated above Theoretically, it would appear that direct vision techniques which allow the operator to visualize his field would be preferable to the "closed" methods To a certain degree, this is true, among survivors, "open heart" procedures have yielded only one-half as many fair and poor results as the "closed" techniques However, the mortality in atrio-septo-pexy and atrial well closures is only slightly more than one-half that of the direct vision procedures

Only Husfeldt[22] has reported serious post-operative complications All of his cases demonstrated reestablishment of the interatrial shunt on post-operative clinical evaluation It is believed that the circumcluding suture pulled through the septal tissue in these cases In view of this, and despite the successful results reported by Bjork and Crafoord,[38] Sondergaard,[35] and others in 1954 and 1955, the technique of circumclusion must be regarded with some degree of suspicion until more cases are available for later post-operative evaluation Perhaps, the reinforcing suture as utilized by McNamara and Cooley[31] and Bosher[30] will prevent transection of the septal tissue by the circumcluding suture and insure complete permanent closure of the defect

It is self-evident that the methods of closure employing circumclusion and the atrial well require highly skilled operators, practiced in the most minute of digital movements Atrio-septo-pexy is perhaps the "closed" method most adaptable to widespread use involving the least special equip-

TABLE V

RESULTS OF SURGICAL CLOSURE OF OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT

Method	Cases	Deaths	Per Cent Mortality	"Good" Results / Total Cases Evaluated
Atrio-septo-pexy	84	5	6 0	44/51
Circumclusion	49	4	8 2	22/25
Atrial Well	49	3	6 1	37/44
Direct Vision	99	11	11 1	56/59
TOTAL	281	23	8 2	159/179

ment and training. Direct vision techniques relieve the surgeon of dependence on tactile sensation, but require highly skilled operating room teams.

At present, the use of hypothermia introduces the possibility of severe cardiac arrhythmias and transient post-operative neuropathies. It is not beyond the realm of probability to assume that vigorous pharmacological and physiological research will soon overcome these complications, but they must be considered in evaluating and comparing present operative techniques.

Utilization of the pump-oxygenator provides the most promise for the future. Here the surgeon can work in an "open heart" for long periods of time. There have been a minimum of post-operative complications in Lillehei's six patients,[57] but a much larger group of cases is needed before this method can be properly evaluated.

Persistent Atrio-Ventricularis Communis

There is still small cause for optimism in the surgical picture of persistent atrio-ventricularis communis. Because of the valvular deformities involved in both the partial and complete forms of this anomaly, it is difficult to understand how "closed" methods of repair, which do not permit suturing of the cleft valve or valves, can lead to "good" results on post-operative evaluation. It must be assumed that the eight cases demonstrating complete abolition of the shunt and regression or loss of symptoms post-operatively as reported in the literature[31-37] were instances of the rare ostium primum defect without involvement of the atrio-ventricular valves or were examples of the situation reported by Cooley and Kirklin where the cleft mitral valve was physiologically competent.

Critical appraisal of the statistics in Table VI verifies the statement that direct vision methods of repair of persistent atrio-ventricularis communis are the only procedures which will benefit the majority of survivors. The lesion is complex and the partial form cannot yet be distinguished from the complete form pre-operatively. Thus, the limited period of

TABLE VI

RESULTS OF SURGICAL CLOSURE OF PERSISTENT ATRIO-VENTRICULARIS COMMUNIS

Method	Cases	Deaths	Per Cent Mortality	"Good" Results / Total Cases Evaluated
Atrio-septo-pexy	21	12	57.1	4/9
Circumclusion	15	2	13.3	3/13
Atrial Well	3	0	0.0	1/3
Direct Vision	34	18	52.9	13/16
TOTAL	73	32	43.8	21/41

inflow and outflow stasis in open cardiotomy under hypothermia is inadequate for identification of the nature of the deformity and its appropriate repair (see Table IV) Cross circulation was abandoned in favor of the pump-oxygenator as a method of cardiopulmonary bypass because of the risk to two patients instead of one The latter instrument has met with high mortality in the first 20 cases It is significant, though, that all 11 survivors demonstrate complete correction of the deformity on post-operative clinical evaluation It seems fair to assume that mortality will decline as the number of cases submitted to surgery increases At this time, however, either form of persistent atrio-ventricularis communis carries only a "50-50" prognosis for recovery from surgery in contrast to a "90-10" prognosis in cases of ostium secundum atrial septal defect

SUMMARY AND CONCLUSIONS

Within the past five years, four techniques of successful surgical correction of defects in the atrial septum have been introduced and employed in significant numbers of cases These include atrio-septo-pexy, circumclusion, closure through an atrial well, and direct vision correction in the "open" heart

A survey of the literature for the three year period 1954 through 1956 disclosed 444 cases of atrial septal defect submitted to surgery and evaluated on a clinical or physiologic basis post-operatively, 281 cases were of the ostium secundum type, 73 cases were of the persistent atrio-ventricularis communis variety (partial or complete forms), and 90 cases were undifferentiated as to type of defect in the published reports

Techniques for surgical closure are described and results as reported in the literature are evaluated All methods of closure of the ostium secundum defects have met with success, the overall mortality in the 281 cases evaluated was 8 2 per cent Direct vision procedures employing hypothermia or a pump-oxygenator to permit stasis of the circulation to and from the heart and thus allow visualization of the defect have yielded the highest percentage of complete closures but are presently associated with the highest mortality rate among the four evaluated techniques The complex nature of persistent atrio-ventricularis communis deformities requires long periods of work in the "open" heart, necessitating use of a pump-oxygenator for cardiopulmonary bypass Results in the first 20 cases are equivocal, there were nine deaths, but the remaining 11 patients all demonstrate complete correction of the deformity

Acknowledgment The author wishes to express his sincere appreciation for the invaluable criticism and guidance of Dr Paul Adams, Jr , Assistant Professor of Pediatrics, University of Minnesota Medical School, without whose encouragement this paper would likely not have been completed

RESUME

Pendant les cinq dernières années, quatre techniques de correction chirurgicale satisfaisante des défauts de la paroi de l'oreillette ont été introduites et utilisées dans un grand nombre de cas Elles comprennent l'atrio-septo-pexie, la compression artérielle, la fermeture à travers la

paroi de l'oreillette et la correction par vision directe dans l'opération a "coeur ouvert"

Une revue de la littérature pendant une période de trois ans, de 1954 à 1956, met en lumière 444 cas de malformations de la paroi de l'oreillette soumises à la chirurgie, et recensées après l'opération sur une base clinique et physiologique 281 cas étaient du groupe de la communication interauriculaire, 73 cas étaient de la variété commune de la persistance du trou de Botal (formes complètes ou partielles) et 90 cas étaient indifférenciés, quant au type de malformation publiée

L'auteur décrit les techniques de fermeture chirurgicale et discute les résultats tels qu'ils sont rapportés dans la littérature Toutes les méthodes de fermeture des communications interauriculaires ont été accomplies avec succès La mortalité moyenne dans les 281 cas fut de 8,2% Les procédés de vision directe utilisant l'hypothermie ou une pompe oxygénatrice pour permettre le maintien de la circulation à l'arrivée et au départ du coeur et la constatation de la malformation ont comporté le pourcentage le plus élevé de fermetures complètes, mais ils sont actuellement redevables du taux de mortalité le plus élevé sur les quatre techniques estimées La nature complexe des malformations lors de la persistance du trou de Botal exige un travail longtemps prolongé à "coeur ouvert" nécessitant l'emploi d'un oxygénateur à pompe pour assurer le transit cardio-pulmonaire Les résultats des premiers vingt cas sont a demi satisfaisants, il y eu neuf décès, mais les onze malades restants ont tous donné la preuve d'une correction complete de leurs malformations

RESUMEN Y CONCLUSIONES

En los pasados cinco años se han introducido y empleado en un número significativo de casos, cuatro técnicas de corrección satisfactoria de los defectos del septum atrial Ellos incluyen la atrio-septo-pexia, la cirnuninclusión, las clausuras a través de un poso atrial y la corrección bajo visión directa en corazón abierto

Una revisión de la literatura para los tres años de 1954 hasta 1956 permitio encontrar 444 casos de defecto atrial septal operados y estimados sobre bases clínicas, y fisiológicas postoperatoriamente, 281 casos fueron del tipo ostium secundum, 73 de la variedad atriventricular común (formas parciales o completas) y 90 fueron indiferenciados respecto del tipo en las publicaciones

Se describen las técnicas de clausura quirúrgica y los resultados segun la literatura se valúan

Todos los métodos para cierre del tipo ostium secundum fueron de buenos resultados, la mortalidad global en 281 casos fué de 8 2 por ciento

Los procedimientos de visión directa usando hipotermia o una bomba con oxigenador para permitir detención de la circulación de y hacia el corazón y así permitir la vista del defecto, han dado el porcentaje mayor de clausuras completas pero por ahora se asocian a la mortalidad mayor entre las cuatro técnicas consideradas

La naturaleza compleja del defecto atriventricular persistente común requiere largo tiempo de trabajo en el corazón abierto necesitándose el

oxigenador con bomba para la desviación de la circulación Los resultados en los primeros 20 casos no son francos porque hubo nueve muertes pero en los 11 restantes, todos obtuvieron completa corrección de la deformidad

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Im Verlauf der letzten 5 Jahre wurden 4 Techniken einer erfolgreichen chirurgischen Behebung von Vorhof-Septumdefekten entwickelt und in einer beträchtlichen Zahl von Fällen zur Anwendung gebracht Zu diesen Verfahren gehören Vorhof-Septum-Anheftung, Zirkumklusion, Verschluss durch eine Vorhofswand und Korrektur unter direkter Sicht am "offenen" Herzen

Eine Literatur-Übersicht der 3-Jahresperiode von 1954 bis Ende 1956 ergab 444 Fälle von Vorhof-Septumdefekt mit chirurgischer Behandlung, die postoperativ auf klinischer oder physiologischer Basis ausgewertet wurden, 281 Fälle gehörten dem Typ des ostium secundum an, 73 Fälle der Varietät des persistierenden gemeinsamen Vorhof-Ventrikels (partielle oder komplette Formen), und 90 Fälle waren in den veröffentlichten Berichten nicht aufgegliedert hinsichtlich der Art des Defektes

Die Methoden für den chirurgischen Verschluss werden beschrieben und die Ergebnisse and Hand der Literatur-Berichte ausgewertet Alle Verfahren des Verschlusses der Ostium-secundem-Defekte waren erfolgreich Die Gesamt-Mortalität der 281 ausgewerteten Fälle betrug 8,2% Die Methoden unter direkter Sicht, die die Unterkühlung oder die Sauerstoff-Versorgung durch Pump-System anwandten zur Ermöglichung eines Stillstandes der Zirkulation zum und vom Herzen und die auf diese Weise die direkte Darstellung des Defektes gestatteten, ergaben den höchsten Prozentsatz kompletter Verschlüsse, sind aber gegenwärtig verknüpft mit den höchsten Mortalitäts-Ziffern der 4 ausgewerteten Prozeduren Die komplexe Naturder persistierenden formitäten des atrio-ventricularis communis erfordert langes Arbeiten am "offenen" Herzen und macht so die Benutzung eines Pumpen-Oxygenators für den cardio-pulmonalen Nebenschluss erforderlich Die Resultate der ersten 20 Fälle sind zweifelhaft mit 9 Todesfällen, während die restlichen 11 Patienten sämtlich eine vollständige Behebung der Missbildung aufwiesen

References will appear in reprints

ELECTROCARDIOGRAM OF THE MONTH

Angina Pectoris and Premature Systoles Induced by Exercise

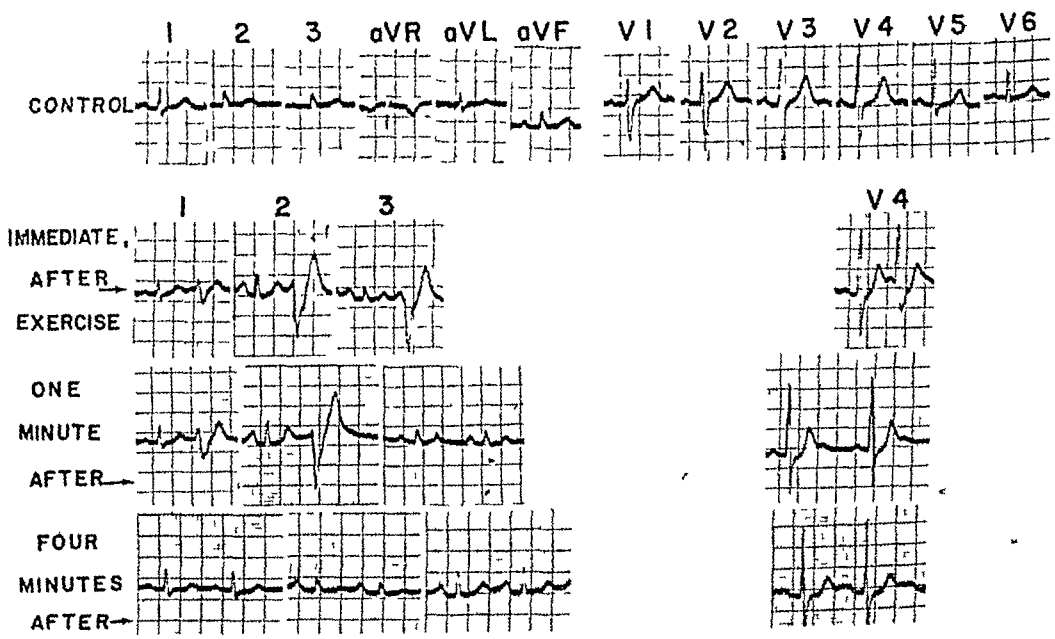
The author would be pleased to receive comment and controversy from readers in relation to explanations offered

A 39 year old railroad brakeman gave a one month history of mid-sternal "raw feeling" radiating to the lower anterior one-third of the neck This sensation was never described as a pain or a pressure It usually occurred after walking a quarter of a mile Sometimes he could walk three miles without this symptom It always disappeared after rest Both parents have heart disease but three brothers do not Physical examination was entirely negative The blood pressure was 130/80

Cardiac fluoroscopy and x-ray showed a normal cardiac silhouette without ventricular enlargement The serum cholesterol was normal The clinical impression was angina pectoris because of the site and radiation of the chief complaint

At this age, collateral evidence is welcome and hence a two step exercise test was performed Immediately after exercise, the S-T segment in Lead IV (see illustration) was depressed almost 1 mm This is abnormal according to Master's criterion but not by the standards of other investigators Hence this finding alone might not be sufficient evidence

Immediately after exercise there developed coupled premature ventricular systoles from one focus constituting a pulsus bigeminus which disappeared after one minute (see illustration) The literature on premature



ventricular systoles, whether coupled or not, produced by exercise is not extensive but the evidence indicates that they are usually, although not invariably, associated with coronary insufficiency They were so interpreted in this patient (who had no previous history of premature contractions) Interestingly enough, the patient developed at the end of the exercise test a "raw feeling" in the midsternum suggesting that this complaint is the "equivalent" of pain for this particular patient

Thus the following data are available a suspicious history and the occurrence of the main complaint after exercise, S T segment depression in a precordial lead, coupled premature ventricular systoles precipitated by the two-step exercise test This evidence was interpreted as corroborating the initial impression of angina pectoris

STEPHEN R ELEK, M D , F C C P *
Los Angeles, California

*Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Co-Chief, Cardiac Clinic, Cedars of Lebanon Hospital, and Consulting Cardiologist, Veterans Administration

Case Report Section

Paroxysmal Pseudoventricular Fibrillation

(Paroxysmal Atrial Fibrillation with Accelerated Atrioventricular Conduction)

KADRI ISIK, M D,* EPAMINONDA SECONDARI, M D, F C C P**
and RICHARD R FERAYORNI, M D†
New York, New York

The present report concerns a patient who was successfully treated for paroxysmal pseudoventricular fibrillation with procaine amide (pronestyl) intravenously This unusual electrocardiographic pattern occurs in healthy young individuals with no clinical evidence of heart diseases Recently, Hermann, et al reported six cases of paroxysmal pseudoventricular fibrillation in young individuals [10]

The patient was a 34 year old white man, admitted to the hospital on February 13, 1957 He complained of palpitation and heaviness in his chest He was well until one hour before admission While talking by telephone, he noted the onset of palpitation There was no dyspnea, chest pain, weakness or dizziness System review was entirely negative His first attack had occurred at the age of 24 while playing basketball Since then similar spells occurred approximately once or twice a year Invariably the attacks were associated with physical activity, would last for a few minutes and disappear after he laid down There was no history of rheumatic fever, chorea, scarlet fever or diphtheria The family history was not contributory He drank two cups of coffee and smoked a package of cigarettes daily Physical examination revealed a well developed young white man in no acute distress There was no cyanosis or dyspnea The temperature was 99° F The radial pulse was 240-260 per minute The examination of the eyes, ears, nose and throat was normal The neck veins were not distended and the thyroid was not enlarged The lungs were normal to auscultation and percussion The heart was not enlarged There were no murmurs or thrills The rhythm was slightly irregular at a rate of 240 per minute The blood pressure was 115 mm Hg systolic and 80 mm Hg diastolic The radial pulse was weak and thready The remainder of the physical examination was essentially negative

The urinalysis was normal The white blood cells numbered 11,600 per cu mm , of the leukocytes the lymphocytes were 16 per cent, the monocytes 7 per cent the neutrophils 69 per cent, stabs 7 per cent, and the eosinophils 15 The sedimentation rate was 26 mm per hour (Westergren)

On admission, the electrocardiogram (Figure 1A) was interpreted as a paroxysmal ventricular tachycardia There was an unusually high ventricular rate of 240 per minute with slight irregularity and many bizarre ventricular complexes Carotid sinus stimulation was ineffective It was decided to give procaine amide (pronestyl) intravenously The initial dose of 200 mg was given slowly with no untoward effects In about 120 minutes the entire dose of 800 mg was given at which time the heart action was restored to the sinus rhythm (Figure 1B) The P-R intervals were very short (0 06-0 08 second) and the initial portion of the up stroke of the R wave was slurred producing a delta R type wave such as is seen in accelerated atrioventricular conduction He had no complaint and it was decided to place him on oral quinidine sulfate 0 2

From the Department of Medicine, Columbus Hospital, New York, N Y
*Formerly Chief Resident in Medicine, Columbus Hospital Present address Westfield, Massachusetts
**Director of Cardiology Department, Columbus Hospital
†Formerly Chief of Medicine, Columbus Hospital Present address Fort Lauderdale, Florida
Acknowledgment We are deeply indebted to Charles Kosmann, M D, New York University, Bellevue Medical Center, for his review of the electrocardiograms

grams four times daily Every other day an electrocardiogram was taken without changes and he recovered completely There was no recurrence of tachycardia during 13 days of hospitalization and he was discharged without any cardiac symptom The heart was not enlarged and no abnormal sound was heard after the attack was over

DISCUSSION

This unusual electrocardiographic pattern occurs in healthy young individuals with no clinical evidence of heart disease, whose only complaints are paroxysmal rapid heart action [7] In spite of these bizarre electrocardiographic findings these patients are comfortable and their blood pressures are well maintained This syndrome is thought to be benign The electrocardiogram pattern may be produced by two conditions, paroxysmal tachycardia with atrial fibrillation in a patient with accelerated A-V conduction and tachycardia with false bundle branch block [10] In 1930 Wolff-Parkinson and White described the syndrome of the short P-R interval with an abnormal QRS complex and paroxysmal tachycardia It occurred especially in young individuals with normal hearts The paroxysmal rapid heart action is always of the supraventricular variety Atrial fibrillation and flutter may also occur [5] Paroxysmal heart action occurs in at least 70 per cent of all cases of the Wolff-Parkinson and White syndrome [7] Prinzmetal et al [5] report experimental and clinical evidence of accelerated conduction through the atrioventricular node Paroxysmal ventricular

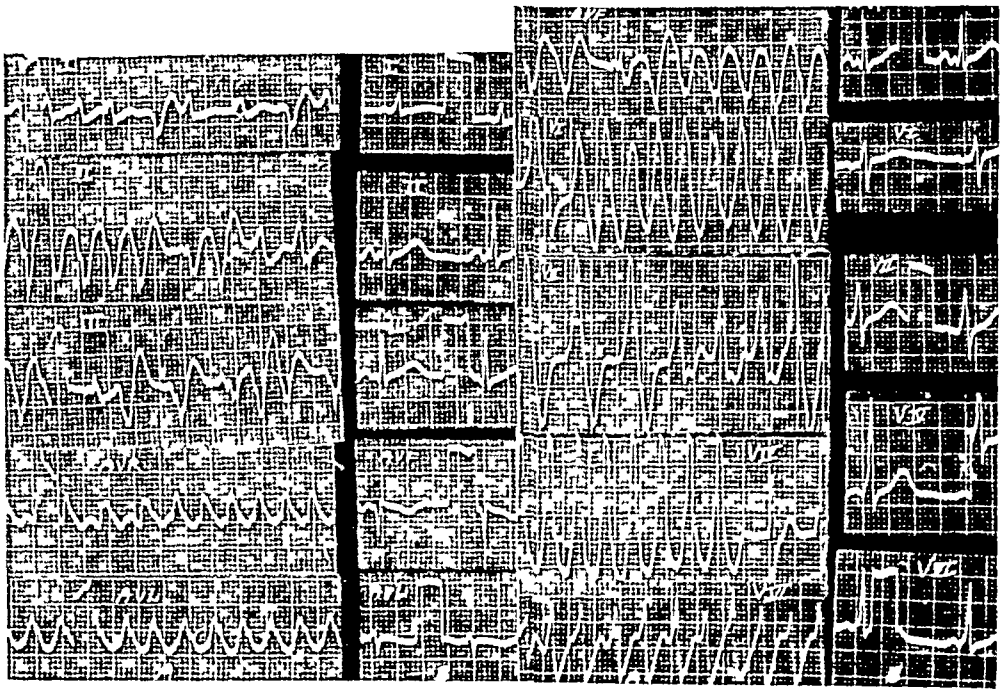


FIGURE 1A FIGURE 1B

Figure 1A Electrocardiogram taken during the attack, showing pseudoventricular fibrillation at the rate of 240 per minute —*Figure 1B* After 800 mgm Procaine Amide (Pronestyl) given intravenously, shows aberrant QRS complexes, short P-R interval, and slurred uptake R-Delta waves, without P-waves showing the underlying atrial fibrillation

tachycardia has been described as of rare occurrence in association with the Woff-Parkinson and White syndrome [9] With ventricular tachycardia the rhythm is practically regular and the P-R interval is constant Carotid stimulation does not affect the rate in ventricular tachycardia, but it may slow or terminate an attack of supraventricular tachycardia [9] The tachycardia of regular rhythm with Wolff-Parkinson and White syndrome and regularly placed P-waves on each wide QRS and the presence of a few narrow QRS complexes are the diagnostic criteria of paroxysmal pseudoventricular tachycardia [10] Absolutely irregular rhythm with no P-waves and occasional short runs of narrow QRS interval with a high ventricular rate of over 200 indicates atrial fibrillation with false bundle branch block or pseudoventricular fibrillation of the Wolff-Parkinson and White syndrome The prognosis is generally excellent but in rare cases, patients have died in paroxysmal tachycardia with fibrillation Procain amide (pronestyl) is the drug of choice and it must be given slowly intravenously

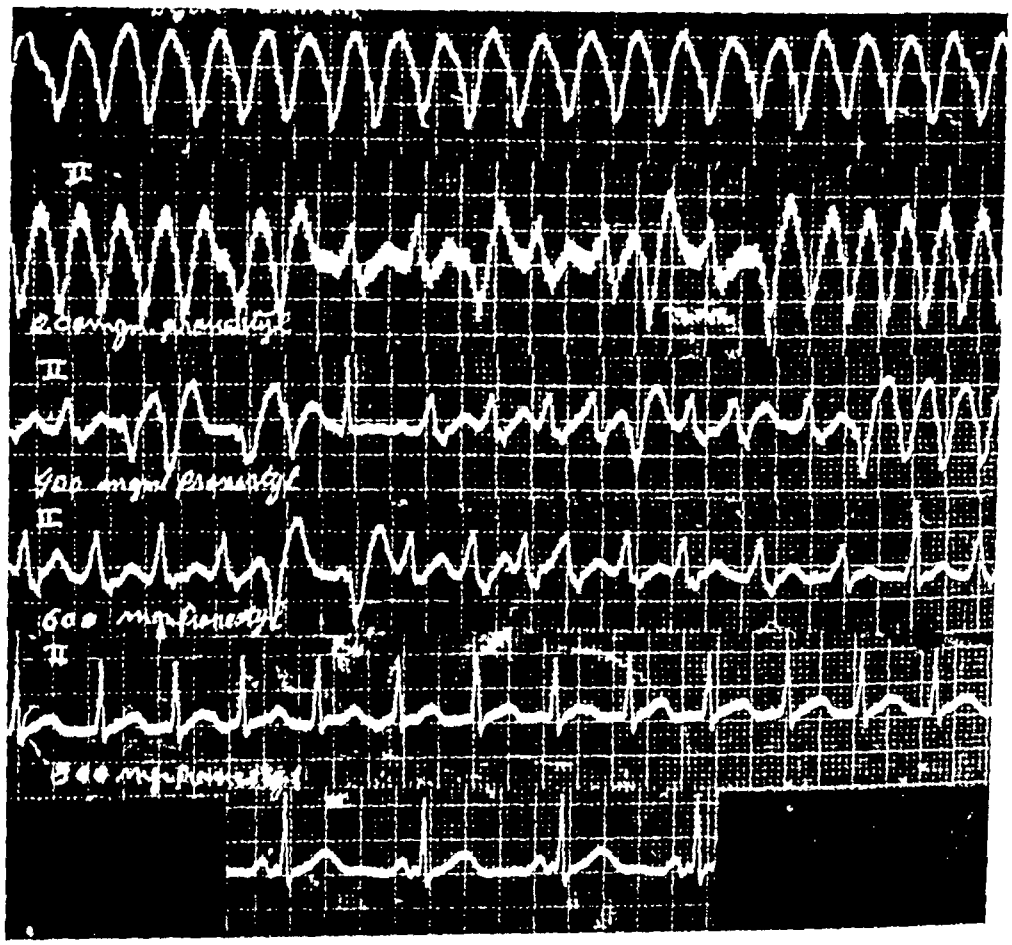


FIGURE 2 Shows Pseudoventricular fibrillation at the rate of 240 per minute Intermittent portions of continuous strip of standard lead II, during intravenous administration of procain amide (pronestyl) After 800 mgm of pronestyl was given, the rate slowed to 140 per minute and an irregular rhythm without P-waves (atrial fibrillation) occurred At the bottom standard lead II shows a normal rhythm with aberrant QRS complexes (slurring of the upstroke of the R-wave) and short P-R intervals (WPW Syndrome)

and with constant electrocardiographic observation and frequent blood pressure determinations Quinidine sulfate may be used but it is our belief that it is dangerous when given intravenously because it may cause cardiac standstill Digitalis should not be given as it may be harmful because of a possible increase of ventricular irritability

REFERENCES

1 Wolff, L, Parkinson, J and White, P D "Bundle Branch Block with short P-R Interval in Healthy Young People Paroxysmal Tachycardia," *Am Heart J*, 5 685, 1930

2 Levine, S A and Beeson, P B "The WPW Syndrome with Paroxysmal of Ventricular Tachycardia," *Am Heart J*, 22 401, 1941

3 Fleishman, S J "A Case of Wolff-Parkinson-White Syndrome with Paroxysmal Ventricular Tachycardia," *Am Heart J*, 44 897, 1952

4 Lyle, A M "Latent Wolf-Parkinson-White Syndrome," *Am Heart J*, 46 49, 1953

5 Prinzmetal, M and Kennamer, R *Accelerated Conduction, the WPW Syndrome and Related Conduction*, New York, 1952, Grune & Stratton Inc

6 Wolff, L "Syndrome of Short P-R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia (WPW Syndrome)," *Circulation*, 10 283, 1954

7 Dunn, J J, Sarell, W and Franklin, R B "The WPW Syndrome Associated with Paroxysmal Ventricular Tachycardia," *Am Heart J*, 47 462, 1954

8 Goldmann, M J "Principles of Clinical Electrocardiography, Accelerated Conduction," 242, 1956, *Lange Medical Publications*, Los Altos, California

9 Friedberg, Ch K *Diseases of the Heart, WPW Syndrome*, 405, 1956 W B Saunder Co Philadelphia, Pennsylvania

10 Hermann, C R, Oates, J R, Runge, T M and Hejtmancik, M R "Paroxysmal Pseudoventricular Fibrillation in Patient with Accelerated A-V Conduction," *Am Heart J*, 53 254, 1957

11 Kosmann, C Personal Communication

Reversible Angina Pectoris*

JACOB D MATIS, M D , F C C P
New York, New York

It has been demonstrated repeatedly that not much importance can be attached to the prognostic significance of bundle branch block Right bundle branch block has been considered to show a more favorable prognosis than left bundle branch block However, the presence of right bundle branch block, either the typical or atypical form, alerts the physician to the basic cardiac disease, particularly disease of the coronary circulation Bundle branch block may occur transiently or it may be permanent Generally, when bundle branch block is associated with coronary atherosclerosis, it is persistent

The following case is reported because of the association of the presence of bundle branch block with symptoms indicative of coronary artery disease and the subsequent disappearance of symptoms and electrocardiographic abnormalities on a specific dietary regimen Of interest are the therapeutic implications associated with the disappearance of symptoms and bundle branch block

The patient was a 46 year old, white pharmacist who presented himself on October 28, 1954 because of an increasingly severe angina pectoris syndrome He stated that for a period of about one year, he had experienced left anterior chest pain with effort The pain usually came on while working and was relieved by sublingual nitroglycerin pills Being a pharmacist, he had tried a number of coronary vasodilator drugs, but none afforded relief He presented himself with regard to limiting hours of work since his tolerance seemed to be decreasing The family history was negative for diabetes and cardiac disease

Examination was not remarkable other than for the presence of xanthoma tuberosum lesions covering the extensor surfaces of both elbows The ocular fundi showed silvering of the arterioles He was 67 inches tall and weighed 164 pounds Blood pressure was 118/68 Heart sounds were normal and no murmur was heard A2 was greater than P2 Examination of the lungs and abdomen was negative An electrocardiogram showed the presence of atypical right bundle branch block Ballistocardiographic study showed an abnormal pattern Laboratory examinations were not revealing other than the cholesterol value of 345 mgm /100 cc of blood

Because of the presence of the xanthoma tuberosum and the elevated blood cholesterol level, he was placed on a low-fat, low-cholesterol diet along with a lipotropic capsule to be taken twice daily When seen two months later, there was no change in symptoms or electrocardiogram findings (Fig 1) He was following the low-fat, low-cholesterol diet and continued to follow it, despite severe restrictions upon his eating habits

On November 7, 1955, the patient reported that he had followed the dietary regimen throughout the year He was no longer having chest pain with effort In addition to his usual, full-time job as a pharmacist, he was doing additional work He now weighed 158 pounds and the physical examination was not remarkable Blood pressure was 144/82 The blood cholesterol was 206 mgm /100 cc of blood Electrocardiographic examination at this time showed a completely normal pattern The right bundle branch block was no longer present (Fig 2) Subsequent examinations have confirmed the presence of a normal electrocardiographic pattern and he remains completely well He has required no nitroglycerin or other medication since following the diet There has been a moderate decrease in the size of the xanthoma tuberosum lesions of his elbow

Etiology of Atherosclerosis

While there has not been a change in the high incidence of atherosclerosis in the United States or in the excessively high death rate due to

*From the Medical Service, Beth David Hospital

atherosclerosis, there has been a marked change in the attitude of physicians towards this disease, physicians and patients alike have assumed a more hopeful outlook Such change in attitude is due to the realization that the concept of atherosclerosis being a physiological aging process is erroneous The present concept of the atherosclerosis problem is the appreciation that it is basically a metabolic disease

There has been a recent realization that atherosclerosis may be preventable or possibly even reversible [1] To reverse the process would result in a tremendous reduction in morbidity and mortality rates in our country as a result of decreasing the incidence of atherosclerosis, the greatest cause of death in the middle aged and elderly [2] All investigations seem to point to the fact that atherosclerosis is primarily a metabolic disease, particularly such metabolism as concerns the cholesterol-lipid-lipoprotein relationship in the human body Although much of the work emphasizes that the typical American diet, which is high in cholesterol, lipids and calories, is an important etiological factor in atherosclerosis, no attempt has been made to incriminate diet as the only operating mechanism Other contributing factors in the pathogenesis of atherosclerosis are heredity, physical activity, stress, sex and other metabolic diseases such as diabetes, nephrosis and familial hypercholesteremia

In attempting to study why man is unique among mammals in his predisposition to form atheromatous patches in blood vessels, attention has been focused on the chemical factors If the abnormalities of lipid composition associated with atherosclerosis are to be altered in the direc-

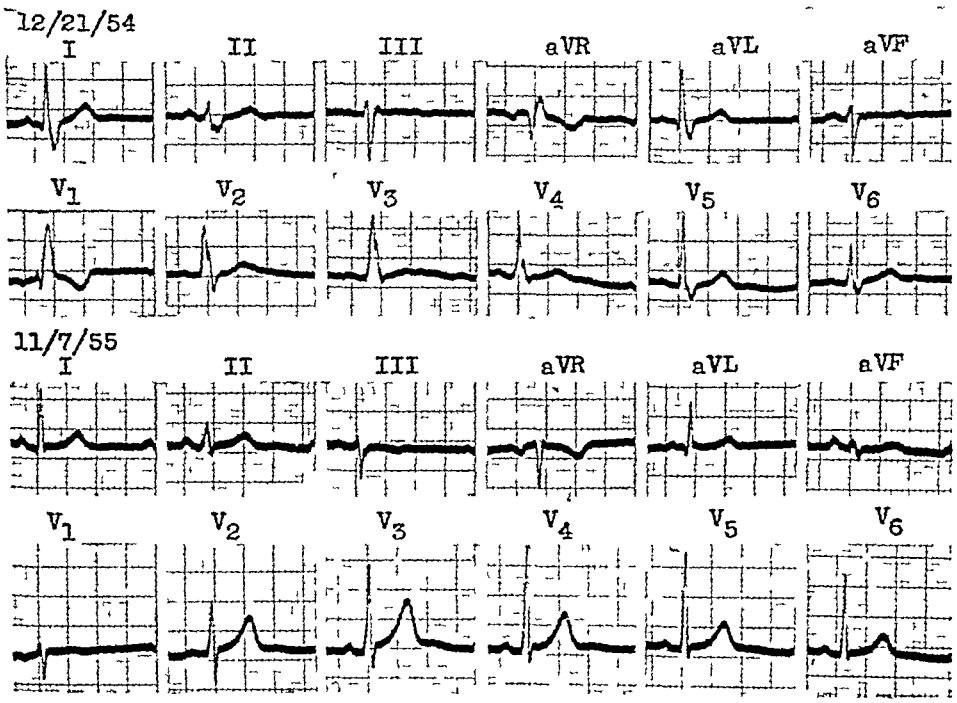


FIG 1

FIG 2

Figure 1 Electrocardiogram taken December 21, 1954 showing atypical right bundle branch block—Wilson type—*Figure 2* Electrocardiogram taken November 7, 1955 showing a normal pattern At this time the patient was free of chest pain.

tion of the conditions found in young women and in mammals immune from atherosclerosis one may use the dietary approach which indicates a low-fat, low-cholesterol diet or follow Ball's approach, which has been the use of female sex hormones [1] While workers previously had attempted to lower serum cholesterol and to alter lipid metabolism by means of diet, the scientific stimulus in this direction resulted from the studies of Keys,[4] who showed that an outstanding feature of all populations known to have relatively little coronary heart disease is the low consumption of fats Experiments in man have shown that fat, and not the cholesterol content of the diet, has a strong effect on blood cholesterol Low-fat diets have also been shown to reduce the incidence of thromboembolic disease In Norway, during World War II, the decline of incidence in coronary artery disease mortality was paralleled by a sharp decline in thromboembolic complications after surgery These declines in mortality and morbidity have been held to be due to the low-fat diet prevalent at the time [4] Another study which indicated a relationship between plasma lipids and coronary atherosclerosis was that of Enos, who reported on American soldiers killed in Korea [5] Gertler's studies also indicated a causal relationship between atherosclerosis and elevated serum cholesterol [6] Confirmation of this study is seen in the studies of H Steiner, who also noted that the high cholesterol level in patients with atherosclerosis fluctuated widely in contrast to the consistently low levels in controls [7] Autopsy studies which reveal a higher incidence of severe atherosclerosis in obese people, confirm the metabolic origin of such atherosclerosis [8]

As a result of these considerations, clinicians have treated patients with atherosclerosis or tendency towards such conditions with low-fat diets While attempts have been made in that direction,[9] [13] achieving a low-cholesterol diet is more difficult and of less value than a low-fat diet Most of the body cholesterol consists of a mixture of exogenous or dietary cholesterol and endogenous cholesterol of hepatic origin Several workers have reported relief of angina pectoris with fat restriction in diet,[10] [11] while others have produced angina pectoris with high fat feedings [12]

Significance of Bundle Branch Block

One of the first articles to stress the benign nature of atypical right bundle branch block appeared in 1934 and described five cases of atypical right bundle branch block, four of whom had no cardiac symptoms, the electrocardiograms remained unchanged over many years with the patients continuing asymptomatic [14] There was little or no evidence of cardiovascular disease on routine physical examination [15] In considering the etiology of bundle branch block, arteriosclerotic heart disease is the common etiological type In a study of 452 cases of bundle branch block[16] either right or left, 31 were examples of benign bundle branch block and these were usually right, the bundle branch block was considered benign when it existed without evidence of organic heart disease The benign type of bundle branch block was thought to be due to benign intercurrent infections. When there is coronary artery disease, the prognosis with

right bundle branch block is better than with left bundle branch block Frequently, either condition is compatible with a long and useful life Wolfran[17] also reported a considerable percentage of cases of bundle branch block unassociated with clinical heart disease, most of the blocks were of right bundle branch type There are reported instances of benign bundle branch block in the same family [18]

In contrast to instances of permanent bundle branch block, there have been a number of reports of transient bundle branch block Transient bundle branch block due to myocardial changes secondary to heart failure has been reported[19] and other workers have reported transitory bundle branch block both in the presence and absence of organic heart disease [20] Bishop[21] followed a case for nine years following an episode of transient left bundle branch block Master reported the presence of transient bundle branch block during an attack of angina pectoris and he suggested that even with septal infarction, bundle branch block may be transitory until collateral circulation has taken place [22] Kalett[23] reported a case of left bundle branch block which existed for four years following coronary occlusion and then disappeared spontaneously, the patient remaining symptom-free This was unusual in that once established, such block is generally permanent

COMMENT

While the exact pathogenesis has not been elucidated, recent studies indicate a close connection between the deposition of cholesterol within the lumen of coronary arteries and the process of atherosclerosis What effect blood cholesterol levels have upon the deposition of cholesterol within the intima of coronary arteries and whether this process can be influenced by exogenous cholesterol is debatable However, it is well known that lowering blood cholesterol levels by means of dietary restriction of fats, frequently causes xanthomatous skin lesions to decrease in size While atheromatous lesions within the intima of arteries need not respond in the exact manner there should be a similar effect

The relief of angina pectoris is generally presumed to be related to improved collateral circulation [5]

In the particular instance herein reported, the association between blood cholesterol levels, electrocardiographic changes indicating cardiac abnormalities and the anginal symptoms cannot be disregarded While the relief of anginal symptoms and the reversion of the pattern of bundle branch block may have been coincidental, the close association of these factors together with a reduction in blood cholesterol and the decrease in size of xanthoma tuberosum lesions achieved by means of reduction in exogenous cholesterol and fats, would indicate a common etiological factor In view of recent experimental studies associating atherosclerosis with cholesterol metabolism, this one case may be a lucid demonstration of such association

REFERENCES

1 Engelberg, H "The Relative Merits of Serum Lipoprotein and Cholesterol Determinations in Atherosclerosis," *J Amer Geriatrics Soc*, 2 146, 1954

2 Katz, L N, Stamler, J and Pick, R "Research Approach to Atherosclerosis," *J A M A*, 161 536, 1956

3 Barr, D P "Some Chemical Factors in the Pathogenesis of Atherosclerosis," *Circulation*, 8 641, 1953

4 Keys, A "Human Atherosclerosis and the Diet," *Circulation*, 5 115, 1952

5 Enos, W F, Beyer, J S and Holmes, R H "Pathogenesis of Coronary Disease in American Soldiers Killed in Korea," *J A M A*, 158 912, 1955

6 Gertler, M M, Garn, M S and Lerman, J "The Interrelationships of Serum Cholesterol, Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease," *Circulation*, 2 205, 1950

7 Steiner, H and Damaski, B "Serum Cholesterol Level in Coronary Arteriosclerosis," *Arch Int Med*, 71 129, 1947

8 Wilens, S L "Bearing of General Nutritional State in Atherosclerosis," *Arch Int Med*, 79 129, 1943

9 LeRoy, G V "Studies of Cholesterol Synthesis in Man," *Ann Int Med*, 44 524, 1956

10 Marrtt, J M and Connor, W E "Idiopathic Hyperlipemia Associated with Coronary Atherosclerosis," *Arch Int Med* 97 492, 1956

11 Malmros, H, Swahn, B and Truedson, E "Essential Hyperlipemia" *Acta Med Scandinav*, 149 91, 1951

12 Duo, P J and Joyner, C F "Angina Pectoris Induced by Fat Ingestion in Patients with Coronary Artery Disease," *J A M A*, 158 1008, 1955

13 Dobbin, Gofman, Jones, Lyon and Young *The Low Fat, Low Cholesterol Diet* Doubleday and Co, Inc, Garden City, N Y 1951

14 Von Dusten, H T and Dolganos, M "Atypical Bundle Branch Block With a Favorable Prognosis," *Am J M Sc*, 188 231, 1934

15 Bayley, R H "The Frequency and Significance of Right Bundle Branch Block," *Am J M Sc*, 188 236, 1934

16 Vazifdar, J P and Levine, S A "Benign Bundle Branch Block," *Arch Int Med*, 89 568, 1952

17 Wolfran, J "Bundle Branch Block Without Significant Heart Disease," *Am. Heart J*, 41 656, 1951

18 DeForest, R E "Four Cases of Benign Left Bundle Branch Block in Same Family," *Am Heart J*, 51 398, 1956

19 Willius, F A and Anderson, M J "Transient, Recurrent Bundle Branch Block," *Am Heart J*, 10 248, 1934

20 Vesell, H "Unstable Bundle Branch Block," *A J M Sc*, 202 198, 1941

21 Bishop, L F "Transient Complete Bundle Branch Block," *Am. Heart J*, 15 354, 1938

22 Master, A M, Dack, S and Jaffe, H "Transient Bundle Branch Block," *Am Heart J*, 16 283, 1938

23 Kalett, J "Bundle Branch Block With Spontaneous Reversion After Four Years," *Am Heart J*, 29 120, 1945

Pulmonary Sporotrichosis

GEORGE W POST, M D , F C C P , ALBERT JACKSON, M D , F C C P
PAULINE E GARBER, M D and GLORIA E VEACH, B S

Wadsworth, Kansas

Routine intradermal sensitivity tests for histoplasmosis and coccidioidomycosis, and not infrequently serological examinations for these infections, have long been recognized as part of the work up of a patient hospitalized with a diagnosis of tuberculosis Sporotrichum infection, however, is not ordinarily expected to become a problem in the differential diagnosis of pulmonary tuberculosis [1] In contrast to histoplasmosis and coccidioidomycosis the occurrence of sporotrichosis as a disease of the lungs without cutaneous involvement is exceedingly rare [2 3 8] Such is the subject of this report

A 53 year old white man was admitted to the Veterans Administration Center, Wadsworth, Kansas, on November 9, 1955, with a history of "lung trouble" for the past five years, which had become worse during the past two years He had to quit farming and cattle feeding because of dyspnea and cough

A chest x-ray film was taken by the State Mobile Unit on October 14, 1955, which showed severe disease throughout the upper two-thirds of the left and the upper third of the right lung Hospitalization was advised by his private physician

He denied having had skin lesions for which he was specifically and repeatedly questioned He had spent all his life near Milford, Kansas, except for a period of Military Service when he was stationed in Colorado (Colorado Springs and Golden)

FIGURE 1

FIGURE 2

Figure 1 Showing fibro-cavitary disease in the upper two-thirds of the left lung and fibrocaseous disease in the upper third of the right lung —*Figure 2* Showing a 4 5 cm cavity in the upper lt lung containing a fluid level and cavity in the left upper lung

From the Veterans Administration Center

He was thin and appeared chronically ill Over the upper half of the left lung resonance was diminished, tactile and vocal fremitus were increased, and there were coarse rales and rhonchi These were also present over the right mid lung posteriorly The blood pressure was 128/72, temperature 98 4, pulse 76, admission weight 124 pounds compared with an average weight of 130 pounds One to two ounces of mucopurulent, yellowish sputum daily were expectorated

On July 1, 1942, a 70 millimeter military induction film showed no evidence of disease On February 3, 1950, there was minimal fibrosis in the left apex, blunting of the costophrenic angles and thinning of the pulmonary markings consistent with emphysema The next film on November 14, 1955, showed fibro-cavitary disease in the upper two-thirds of the left and fibrocaseous disease in the upper third of the right lung (Figure 1) A planigram on January 1, 1956, showed cavitation in the left and possible honey-combing in the mid portion of the right lung Subsequently there was rapid bilateral progression of the disease until the film of March 7, 1956 (Figure 2), showed a 4 5 cm cavity in the upper lobe of the right lung containing a fluid level as well as the previously seen cavity in the upper lobe of the left lung X-ray film on April 6, 1956, showed regression for the first time which was more pronounced in the right lung (one month after the start of potassium iodide therapy) On October 25, 1956, a planigram of the left apex showed a 3 x 6 cm cavity (Figure 3) No definite cavity was seen on a planigram through the right apex at this time

There were no cutaneous or lymphatic lesions visible or palpable Upper and lower GI series were negative An x-ray survey of the lung bones of the upper and lower extremities was negative Sigmoidoscopic examination was negative except for small benign polyps which were fulgurated

Serological examinations for tularemia, brucellosis, typhoid, para-typhoid, and syphilis were negative A complement fixation test for histoplasmosis performed in Fulcolow's Laboratory (Kansas City Field Station, USPHS) was positive in January, 1956, with a titer of 1 8 A repeat test within eight weeks was negative Intradermal sensitivity tests were negative using intermediate and second strength PPD, histoplasmin 1 500, coccidioidin 1 100, and blastomycin 1 100 Sixteen sputum cultures for acid fast bacilli were negative

Twelve sputum cultures for fungi were positive for Sporotrichum After five days of growth at 37°C, and after seven days of growth at room temperature, on brain heart infusion glucose blood agar, the typical yeast phase of Sporotrichum schenckii (Figure 4) was obtained After 14 days of growth at room temperature on the same medium, the culture showed the yeast phase and mycelium formation at the edge of

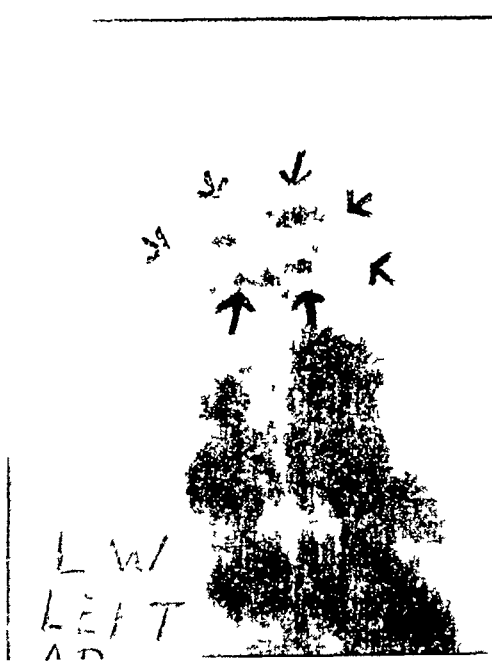


FIGURE 3

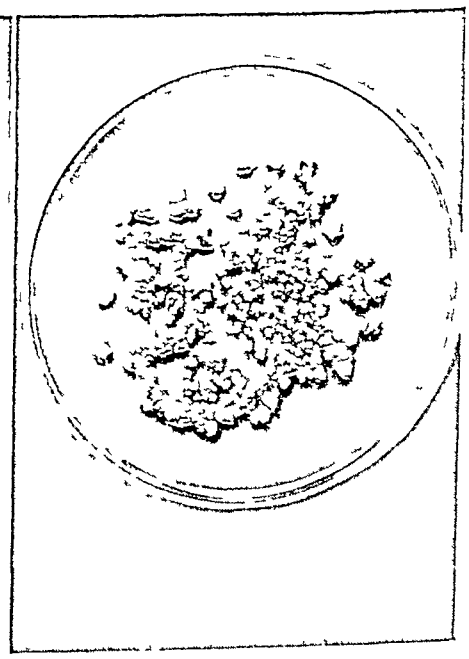


FIGURE 4

Figure 3 Showing a 3 x 6 cm left cavity — *Figure 4* Showing the yeast phase of Sporotrichum schenckii

the colony (Figure 5) An intraperitoneal mouse inoculation with one of the positive yeast phase cultures was positive for Sporotrichum schenckii (Figure 6) Identity of the organisms was confirmed by the Veterans Administration Area Reference Laboratory in St Louis, Missouri Serological examinations performed by Walter Reed Army Institute were reported as follows Histoplasmin whole yeast phase antigen negative, blastomycin yeast phase positive with titer of 1 8, coccidioidin negative, sporotrichum yeast phase positive with titer of 1 64 Agglutination tests approximately two months apart were positive for sporotrichosis with a titer of 1 320 in Conant's Laboratory, Duke University School of Medicine The cigar-shaped gram-positive bodies of Sporotrichum were also demonstrated on direct smears of sputum

Bronchoscopy on March 5, 1956, showed no intrinsic bronchial lesions, but thick secretions were present in the left main bronchus Examination of the washings for malignant cells was negative A culture of the washings was sterile for acid fast bacilli and positive for Sporotrichum schenckii

The Sporotrichum was cultured on media containing isoniazid and streptomycin to see whether the organisms would show a more abundant growth in the presence of these drugs This was done because of the initial rapid spread of the disease during INH and PAS therapy However, there was no noticeable difference in the growth on Thompson's medium (brain heart infusion glucose blood agar with 20 units of penicillin per milliliter and 40 units of streptomycin per milliliter)

After the initial positive sputum cultures for Sporotrichum were obtained, monthly cultures were performed Except for negative cultures for sporotrichum in February and March of 1957, all other cultures, including the most recent one of June 1957, were positive

Since the presumptive diagnosis on admission was pulmonary tuberculosis, chemotherapy was started on November 22, 1955, using INH 300 mg daily and PAS 12 gms daily In addition 500,000 units of penicillin was given daily for six days and achromycin was given in a dosage of one gram daily for 17 days Saturated solution of potassium iodide was started March 6, 1956, after sporotrichosis had been definitely diagnosed and tuberculosis ruled out Isoniazid and PAS were discontinued The dose of saturated solution of potassium iodide was gradually increased to 216 drops daily Dihydroxystilbamadine was given intravenously during the early months of treatment concurrently with the administration of potassium iodide A total dosage of 3,825 mgs of dihydroxystilbamadine was given between April 20, 1956, and June 1, 1956 It was then discontinued because of unpleasant side reactions following the intravenous injections [4]

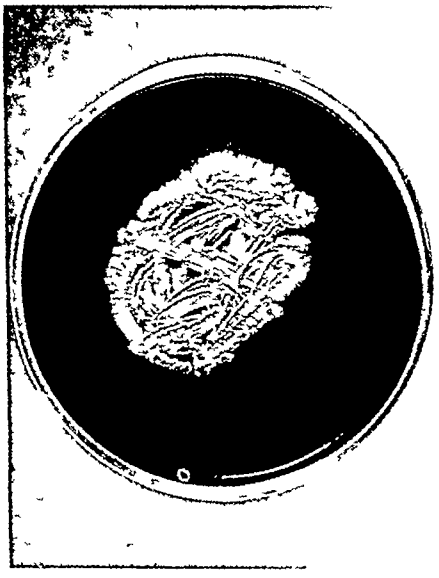


FIGURE 5

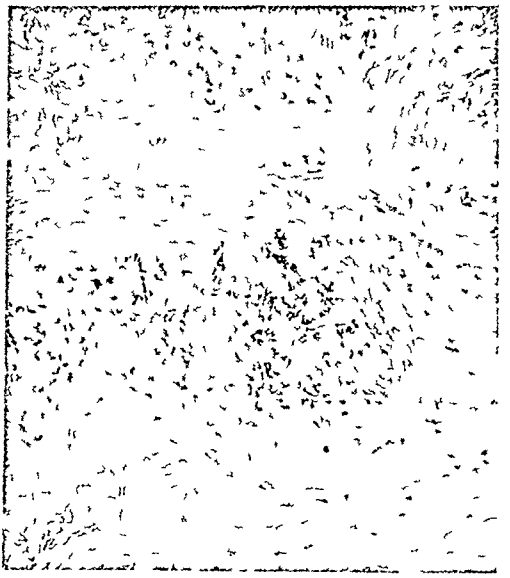


FIGURE 6

Figure 5 Showing the yeast phase and mycelium formation at the edge of the colony after 14 days of growth —*Figure 6* Mesentery of a mouse inoculated with yeast phase culture, showing Sporotrichum schenckii (Gram stain) (magnification 480X)

The weight remained stable at about 128 pounds between November 1955 and April 1956 However, between April 1956 and December 1956, there was a 21 pound weight gain from 128 to 149 pounds During the first month of hospitalization the temperature varied from within normal limits to maximums of 99° F A maximum of 100 was reached on two occasions Subsequently there were occasional temperature elevations to 99° F (July 1957)

Treatment with amphotericin B is contemplated in view of the fact that the treatment with potassium iodide failed to result in negative sputum cultures for Sporotrichum schenckii

DISCUSSION

When sporotrichosis is diagnosed, it is usually found as a disease of the skin, mucous membranes, lymphatic tissues, viscera, or bones or any combination of these [5] The usual port of entry for the fungus of sporotrichosis is a wound of the hand (this is a disease common in gardeners, for example) causing cutaneous lesions and from there the fungus can spread via the lymphatics and cause visceral involvement

If the sputum harbors Sporotrichum, the latter can be demonstrated also by direct smear of the sputum Our patient had a positive direct smear of the sputum for sporotrichum Webster and Willander described recently a case of sporotrichosis of the knee in which the aspirate was positive for sporotrichosis on direct smear [6]

Localized and disseminated forms of the disease have been recognized Cases of cutaneous sporotrichosis with visceral manifestations, while not being frequent, are not rare [7] Visceral involvement alone appears to be uncommon Sporotrichosis localized to the lungs alone, without other visceral localization, is exceedingly rare To the best of our knowledge we have been able to find, in the world literature, only nine cases of sporotrichosis limited to the lungs [8]

There can be no doubt about the diagnosis of pulmonary sporotrichosis in the present case, since all Koch's postulates have been fulfilled

Immunological procedures may be an aid in diagnosis It is known that complement fixation methods between Histoplasma capsulatum, Blastomyces dermatitidis, Candida albicans, Coccidioides immitis give positive cross reactions [9] There are also frequent positive cross reactions between histoplasmosis and blastomycosis (Emmons and co-workers found that a dilution of 1 100 of histoplasmin gave a positive reaction in guinea pigs with blastomycosis, coccidioidomycosis and that, likewise, patients did react to both histoplasmin and blastomycin [10]) Also positive cross reaction between Sporotrichum schenckii and several strains of pneumococci have been reported [11]

Routine serological tests in our patient showed positive cross reaction between histoplasmosis and blastomycosis The fact that the patient had a positive reaction for blastomycosis aroused our suspicion that he might harbor blastomycosis or any other fungus disease because of a possible cross reaction and a careful search for fungi, including sporotrichosis, was therefore made

This case again exemplifies the fact that if a patient presents himself with an obscure lung condition an intensive search for sporotrichosis,

even if it is rare and unlikely to be found, should be included in the routine work up of the patient, because as D T Smith puts it " and from time to time the investigators will be rewarded with an unusual diagnosis—even a case of pulmonary sporotrichosis " [8]

REFERENCES

1 Smith, D T "Problems in the Diagnosis of Pulmonary Mycoses," *Texas State J Med*, 51 787, 1955

2 Forbus, W D "Pulmonary Sporotrichosis," *Am Rev Tuberc*, 16 599, 1927

3 Trocome, P, Pichevin, A and Boidat, S "Un Case De Sporotrichose Bronchopulmonaire et Cutanee," *J Francais De Med Et Chir Thoraciques*, 4 570, 1950

4 Geraci, J E, Dry, T J, Ulrich, J A, Weed, L A, MacCarty, C S and Sayre, G P "Experiences with 2-Hydroxystilbamadine in Systemic Sporotrichosis," *A M A Arch Int Med*, 96 478, 1955

5 Conant, N F, Smith, D T, Baker, R D, Calloway, J L and Martin, D S *Manual of Clinical Mycology*, 2nd Edition, 1954, W B Saunders Co pp 222-238

6 Webster, F S and Willander, D "Chronic Sporotrichal Synovitis of the Knee," *J Bone and Joint Surg*, 39A 207, 1957

7 Singer, J I and Muncie, J E "Sporotrichosis, Etiologic Considerations and Report of Additional Cases from New York," *New York State J Med*, 52 2147, 1952

8 Smith, D T *In The Chest*, Edited by J A Myers, Charles C Thomas, Publisher, Springfield, Illinois First Edition, 1948 Pp 702-704

9 Salvin, S B "The Serologic Relationship of Fungus Antigens," *J Lab and Clin Med*, 34 1096, 1949

10 Emmons, C W, Olson, B J and Eldridge, W W "Studies of the Role of Fungi in Pulmonary Disease," *Pub Health Rep*, 60 1383, 1945

11 Neill, J M, Castillo, C G and Pinks, A H "Serological Relationships Between Fungi and Bacteria," *J Immunol*, 74 120, 1955

Editorial

Peace. A Task for the Medical World

In all primitive races the practice of medicine and the priesthood were closely related and the same person entrusted with both the interpretation and application of divine manifestations to the welfare of mankind For this office the wisest of the tribe were chosen To rule the tribe and to organize it for war, the bravest and most cunning rather than the most sensitive and intelligent were selected

According to our current interpretation of primitive sociology we assume that the earliest human professions were Priest-Physician and Politician-Warrior Attempts to explain the inscrutable mystery of Creation through metaphysical and philosophical reasoning gradually disclosed two roles in the search for truth and its application for the benefit of mankind those of the true priest and the objective physician The priest deciphers spiritual matters, judges deviations, and seeks healing or comfort by supernatural means The physician searches the expression of the handiwork of the Creator, the ultimate truth, in the morphological and functional aspects of nature By deduction and experimentation he seeks to understand the normal or healthy state of man and also the intrinsic and extrinsic factors and agents which produce the abnormal or diseased state He dedicates his life to the prevention and cure of disease

The objective of the clergy is to sustain the eminence of man on the basis of faith, the metaphysics of which is not within the comprehension of many and therefore must be supported by the incontestable pronouncements of dogma The strong bonds of religion will unify great masses of people, the tenets of which however are not now, and perhaps never will be, amenable to objective reasoning

The physician studies and serves the most valuable and perfect product of Creation Man Fundamentally identical in all the world, the differences in race or traits are insignificant when one considers genetic factors, structure and function The common devotion to the welfare of mankind gives the medical profession a stamp of fraternity In every country the physician finds colleagues who have the same basic interest in humanity and who pursue the common task of defending the life and health of others

I have visited and lived in countries on five continents with inhabitants of many races having different degrees of progress, cultural traditions, economic conditions and religious beliefs By this experience I have confirmed the extraordinary similarity of the attitude of one physician to another, of the physician to the community, and the community to the physician The fundamental reason for this unity of spirit is that the brain and the heart, like all the cells of our functional system whether serving the basic vegetative functions or highly specialized to give each of us an individual character, are essentially the same for all human beings This casts the physician in a privileged role, namely that of uniting

the people of the world for the most positive of all reasons, the conservation of life and health Wars occur because of negative factors, dissimilarity in political or religious views and disagreement over the interplay of economic power Atomic energy, a new and powerful tool, has recently become available to man In the hands of some politicians who are enemies of freedom and human tolerance, it is a negative force jeopardizing the future of the human race In the hands of the world's physicians, this same power has already become a significant positive factor for health and peace Common ground to unite the world on a religious, political, or economic basis may never be found Brotherhood is possible however, *through worldwide interest in a unique positive factor*, the preservation of man's most precious gift Life We physicians are by natural right the apostles of this campaign

OVIDIO GARCIA-ROSELL, M D, F C C P*
Lima, Peru

* Regent for Peru

COLLEGE INTERIM SESSION AND SEMI-ANNUAL MEETING, BOARD OF REGENTS

The Interim Session of the College will be held in Rochester, Minnesota, November 29, 30 and the morning of December 1 Headquarters will be at the Kahler Hotel where round table luncheons will be held The scientific sessions will take place in Plummer Hall and Mann Hall of the Mayo Clinic buildings Fireside Conferences will be held in the Mayo Foundation House There will also be tours of the Mayo Clinic, technical exhibits, examinations for Fellowship, dinner and dancing and four motion picture sessions The Semi-Annual meeting of the Board of Regents and Board of Governors of the College will be held at the Hotel Radisson in Minneapolis, December 1 Following is the preliminary program for the meeting

Saturday, November 29

Thoracic and Cardiovascular Surgical Clinics
Methodist Hospital—O Theron Clagett
St Mary's Hospital—John W Kirklin, D C McGoon

Pulmonary Section—Plummer Hall, 2 00 p m

Newer Developments in the Chemotherapy of Tuberculosis
Martin J FitzPatrick, Kansas City, Kansas

Current Standards for Surgical Therapy of Tuberculosis
John B Grow, Denver, Colorado

A Serologic Test for Diagnosis of Tuberculosis
Guy P Youmans, Chicago, Illinois

Surgery of the Trachea and Bronchi
Donald L Paulson, Dallas, Texas

Recent Developments in the Management of Fungous Diseases
Michael L Furcolow, Kansas City, Kansas

Recent Evaluations of Sarcoidosis
Harold L Israel, Philadelphia, Pennsylvania

Cardiac Section—Mann Hall, 2 00 p m

Clinical Manifestation of Several Types of Tricuspid Valvular Disease
Oglesby Paul, Chicago, Illinois

Femoral Artery Blood Flow
D J Ferguson, Minneapolis, Minnesota

Hypothermia for Intracardiac Surgery
F John Lewis, Chicago, Illinois

Diagnostic Application of Indicator-Dilution Curves using a Central Sampling Technic
H J C Swan, Rochester, Minnesota

Experience with Chlorothiazide in the Management of Hypertension
Robert L Grissom, Omaha, Nebraska

Sunday, November 30

Optional tours of medical buildings in Rochester

Round Table Luncheons

Disorders of Esophageal Motility
Moderator Charles F Code, Rochester, Minnesota

Bronchography, Indications and Techniques
Moderator Sheldon E Domm, Knoxville, Tennessee

Surgical Treatment of Acquired Valvular Heart Disease
Moderator Robert P Glover, Philadelphia, Pennsylvania

Early Detection of Emphysema
Moderator Peter A Theodos, Philadelphia, Pennsylvania

Scientific Session

Intrathoracic Complications of Subphrenic Infection
David P Boyd, Boston, Massachusetts
Clinical Application of the Carbon Monoxide Method of Estimating Diffusion Capacity of the Lungs
David W Cugell, Chicago, Illinois
Current Thoughts on Asthma
John M Sheldon, Ann Arbor, Michigan
The Staphylococcus 1959 Nemesis
Robert J Anderson, Atlanta, Georgia
Current Concepts of Interstitial Pulmonary Fibrosis
Howard S Van Ordstrand, Cleveland, Ohio

Fireside Conferences and Local Discussors

The Lung in Systemic Disease
F E Donoghue, Rochester
Pulmonary Function Tests and their Utilization
Ward S Fowler, Rochester
Chemotherapy of Tuberculosis
David T Carr, Rochester
Allergy in Pulmonary Diseases
Louis E Prickman, Rochester
Carcinoma of the Lung
O T Clagett, Rochester
Pulmonary Hypertension
Howard B Burchell, Rochester
Diagnostic and Surgical Methods in Intracardiac Septal Defect
R O Brandenburg, Rochester
Medical and Emotional Rehabilitation following Myocardial Infarction
Richard M Steinhilber, Rochester
Techniques in Cardiac Diagnosis (Roentgenologic, catheterization, etc)
Earl H Wood, Rochester
Specific and Non-specific Therapeutic Approaches to Congestive Heart Failure
R L Parker, Rochester

Monday, December 1—Rochester—Mann Hall

Mayo Clinic Chest Conference—Diagnostic Problems
Herman J Moersch, Rochester, Chairman
Cardiac Conference—Clinicopathologic Conference
J E Edwards, Rochester, Chairman
Thoracic and Cardiovascular Surgical Clinics
F H Ellis and P E Bernatz, Rochester

Minneapolis

Chartered buses will leave Rochester at 1 00 p m to arrive in Minneapolis in advance of the sessions to begin at 3 30 p m

Meeting, Board of Regents and Board of Governors

Dinner and panel discussion—"Inhalation Therapy"

Moderator Edwin R Levine, Chicago, Illinois

Panel Seymour M Farber, San Francisco, California, H F Helmholz, Rochester, William F Miller, Dallas, Texas, Maurice S Segal, Boston, Massachusetts

Dr R Drew Miller, Chairman, Pulmonary Section, and Dr Raymond D Pruitt, Chairman, Cardiac Section, Committee on Scientific Program for the Interim Session, have announced that the complete program will be published in the November issue of *Diseases of the Chest* Physicians planning to attend the meetings are requested to write directly to the Kahler Hotel in Rochester and the Hotel Radisson in Minneapolis for reservations, giving arrival and departure dates The Clinical Meeting of the American Medical Association will take place in Minneapolis, December 2-5

College Chapter News

SOUTHERN CHAPTER

The 15th annual meeting of the Southern Chapter, comprised of the 16 southern states and the District of Columbia, will be held in conjunction with the meeting of the Louisiana Chapter, at the Jung Hotel, New Orleans, November 2 and 3. The following program will be presented:

Sunday, November 2—Morning Session

A. H. Russakoff, Birmingham, Alabama, presiding

9:25 a.m. Introductory remarks
Joseph S. Cruise, Atlanta, Georgia, President, Southern Chapter

9:30 a.m. "Roentgen Aspects of Active Histoplasmosis"
Earl E. Little, Jr., Little Rock, Arkansas

"Some Problems of Staphylococcal Pneumonia"
Charles A. Le Maistre, Atlanta, Georgia

"An Appraisal of the Clinical Value of Prolonged Positive Pressure Breathing"
Ben V. Branscomb, Birmingham, Alabama

"A Clinical Study of Chronic Pulmonary Disease due to Atypical Mycobacteria"
Albert G. Lewis, Jr., Tampa, Florida

"Pulmonary Fibrosis: A Histochemical Approach"
A. E. Anderson, Jr., Jacksonville, Florida

Afternoon Session

Robert R. Shaw, Dallas, Texas, presiding

2:00 p.m. "Respiratory Difficulties Associated with Anomalies of the Aortic Arch"
J. Walter Park, III, and Sam Greer, San Antonio, Texas

"Thoracic Surgical Conditions in Infants"
E. S. Crossett, El Paso, Texas

"The Problem of Persistent Positive Sputum after Resection for Pulmonary Tuberculosis"
Clyde Rush, Sanatorium, Texas

"Esophagodiverticulostomy for Stenosis of Upper Esophagus Associated with Zenker's Diverticulum"
Edward F. Skinner and Gene Page, Memphis, Tennessee

"Substitution Operation for Esophageal Strictures"
Osler A. Abbott, Atlanta, Georgia

"Surgical Treatment of Bronchogenic Carcinoma"
G. V. Brindley, Jr., Temple, Texas

6:00 p.m. Cocktail party

Monday, November 3—Morning Session

Frank W. Pickell, Baton Rouge, Louisiana, Louisiana Chapter President, presiding

8:55 a.m. Introduction of Daniel E. Jenkins, Houston, Texas, First Vice President, Southern Chapter

9:00 a.m. "Cardiovascular Research in Britain and in Russia"
T. J. Reeves, Birmingham, Alabama

"Problems in Diagnosis and Treatment of Patent Ductus Arteriosus"
Robert G. Ellison, Augusta, Georgia

"Metabolism of the Isolated Heart"
Watts R. Webb and S. S. Lee, Jackson, Mississippi

"Experiences in the Surgical Management of Tumors of the Chest Wall"
Harold C Spear, DeWitt C Daughtry, and John G Chesney, Miami, Florida

Fifth Annual Paul Turner Memorial Lecture—"Bronchogenic Carcinoma"
Alton Ochsner, New Orleans, Louisiana

Afternoon Session

2 00 p m Symposium "What Do the Newer Research Tools in Cardiovascular Disease Hold for Future Application?"
Moderator George E Burch, New Orleans, Louisiana

Ballistocardiography and Kinetocardiography
E E Eddleman, Birmingham, Alabama

Left Heart Catheterization
T J Reeves, Birmingham, Alabama

Electrocardiography and Kinetocardiography
Manuel Gardberg, New Orleans, Louisiana

POTOMAC CHAPTER

The Potomac Chapter, representing Maryland, West Virginia, and the District of Columbia, will present its annual meeting at the Statler Hilton Hotel, Washington, D C on November 23 The following program will be presented

Roy G Klepser, Washington, D C, chapter president, presiding

8 45 a m Registration

9 15 a m Business Meeting

9 30 a m Symposium "Staphylococcal Pneumonia and its Complications'
Moderator Milton Gusack, Washington, D C

Clinical and Radiographic Aspects
Joseph M Lo Presti, Washington, D C

Surgical Implications
Edgar W Davis, Washington, D C

Symposium "Current Controversies in Pulmonary Tuberculosis—The Duration of Chemotherapy, Problems of Bacterial Resistance and Relapse, The Question of Early Surgery, Management of the 'Open Negative'"
Moderator Sol Katz, Washington, D C

Panel Oscar Auerbach, East Orange, New Jersey, J Maxwell Chamberlain, New York City, Richard F Kieffer, Baltimore, Maryland, James W Raleigh, Sunmount, New York

12 00 noon Round table luncheon panels

A) "Which Antibiotic? Factors Influencing One's Choice"
Moderator John P Utz, Bethesda, Maryland

B) "Anesthetic Problems in Cardiac Surgery"
Moderator Charles E Fierst, Washington, D C

C) "Bronchial Carcinoma Preventable? Treatable?"
Moderator Oscar Auerbach, East Orange, New Jersey

Afternoon session—Cardiovascular Seminar

William L Cooke, Charleston, West Virginia, Vice President, presiding

1 00 p m "Unusual Causes of Heart Failure"
Thomas W Mattingly, Washington, D C

Symposium "Diagnostic Methods in the Study of Circulatory Shunts"
Moderator Andrew G Morrow, Bethesda, Maryland

Panel Eugene Braunwald, Robert Frye, and Robert Long, Bethesda, Maryland

Fireside Conferences

"Coronary Artery Disease"
Benjamin Manchester, Washington, D C

"Emphysema"
James P Mann, Washington, D C

"Esophageal Diseases"
Morris H O'Dell, Charleston, West Virginia

"Clues and Red Herrings in Congenital Heart Disease"
Bernard J Walsh, Washington, D C

MINNESOTA CHAPTER

Newly elected officers of the Minnesota Chapter are

President	J Paul Medelman, St Paul
Vice-President	Sumner S Cohen, Oak Terrace
Secretary-Treasurer	Coleman B Connolly, St Paul

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter will be held on Sunday, October 12 in the Flemish Room of the Jefferson Hotel, Richmond, Virginia

PACIFIC NORTHWEST CHAPTER

The Willow Chest Centre, Vancouver, British Columbia will be the location for the annual meeting of the Pacific Northwest Chapter, November 7-8

RIO GRANDE DO SUL CHAPTER

In cooperation with the Tuberculosis Society of Rio Grande do Sul and the Liga Rio Grandense Contra a Tuberculose, the Rio Grande do Sul Chapter of the College celebrated "Tuberculosis Week" in Porto Alegre on May 17 Professor Carlos Bento, Governor for the College, presided at the opening session held in the Governor's Palace, and spoke on the activities of the three organizations Professor Bento also represented the College at the dedication ceremonies of a new rehabilitation center for tuberculosis patients at the Hospital do Partenon

ANNOUNCEMENTS

The Southern Thoracic Surgical Association will hold its annual meeting at the Deauville Hotel, Miami Beach, Florida, November 28-30, 1958

The School for Inhalation Therapists of St Elizabeth Hospital, Elizabeth, New Jersey, announces the beginning of its Second Academic Sessions on October 14 The course will consist of lectures and demonstrations two mornings each week for six months Further information may be obtained by writing to Dr Burton M Cohen, c/o Mr B R Rosa, Supervisor, Inhalation Therapy Service, St Elizabeth's Hospital, Elizabeth, New Jersey

DISEASES of the CHEST

VOLUME XXXIV NOVEMBER, 1958 NUMBER 5

Sensitivity to Tuberculin, Histoplasmin and Coccidioidin Among High School Students in Northwestern Georgia*

PHYLLIS Q EDWARDS, M D, CECIL F JACOBS, M D
Washington, D C
and DOROTHY BARFIELD, R N
Dalton, Georgia

Skin testing surveys of school-age groups with tuberculin and, in some localities, also with histoplasmin and coccidioidin, are gaining recognition as a useful public health procedure The rapidly changing tuberculosis picture in most communities, together with the apparent need to reduce radiation exposure to a minimum, means that the tuberculin test is emerging as an important method for measuring the progress of tuberculosis control programs Testing, in addition, with fungus antigens is becoming more or less mandatory in areas where fungus infections complicate the picture

The present report adds to the growing body of experience collected during the last few years on the value to a community of results obtained from a carefully conducted skin-testing survey of school-age populations [1 9] The immediate stimulus to undertake the survey arose during the course of reviewing the tuberculosis case register at the Dalton-Whitfield and Murray County Health Department Some of the patients on the register had had repeatedly negative sputum examinations for tubercle bacilli and some, in addition, did not react to tuberculin The high frequency of pulmonary calcifications on routine x-ray films, which could not be attributed to tuberculosis, created a great deal of speculation as to the etiological factor Histoplasmosis came to mind as a diagnostic possibility, as the Whitfield-Murray area is situated in the northwestern corner of Georgia on the fringe of the histoplasmosis endemic area, yet the prevalence of infection with the fungus in the immediate vicinity of Whitfield County was not known The time had come to find out

Study Population and Procedures

The skin-testing survey, supplemented with 70 mm x-ray films, was carried out in March, 1957 It was organized by the Dalton-Whitfield

*From the Tuberculosis Program, Division of Special Health Services, Public Health Service, U S Department of Health, Education and Welfare, and the Dalton-Whitfield and Murray Counties Health Department, Dalton, Georgia

Copyright 1958 by the American College of Chest Physicians

County and Murray County Health Departments A note signed by the District Director of Public Health was sent to the parents of all high school students informing them that during a specified two-week period a survey would be conducted for the purpose of finding out how many students had had tuberculosis or fungus infection, and that a representative of the Health Department would be at each school during the survey to answer questions the students or parents might have about the program A brief statement accompanying the note, and newspaper articles, described the general characteristics of histoplasmosis and coccidioidmycosis and why the Health authorities need to distinguish between these two fungus infections and tuberculosis Mr Clifford Hale, Superintendent of Dalton schools, Mr Albert Davis, Superintendent of Whitfield County Schools, Mr Ray Bagley, Superintendent of Murray County Schools, and all school principals gave their enthusiastic support which assured the success of the project

The survey included the six public high schools in the two counties (fig 1) Two of the schools are located in Dalton Dalton High, for white students living in the city, and Emory High for all Negro students in both Whitfield and Murray Counties White students living in the rural parts of the area attend one of the four rural high schools, whichever is nearest their home The total enrollment for the six schools, as shown in table 1, was estimated to be just over 2,400, and 2,112 (87 3 per cent) of the students were tested and x-rayed Participation was highest, almost 95 per cent, in Valley Point High School and just over 80 per cent in both Murray and Emory High Schools

The testing and reading was done by a field research team from the Tuberculosis Program of the Public Health Service Each student was tested simultaneously with histoplasmin, coccidioidin and tuberculin Two

TABLE I

NUMBER OF STUDENTS ENROLLED, AND NUMBER AND PER CENT WITH COMPLETED TESTS, FOR THE SIX HIGH SCHOOLS IN WHITFIELD-MURRAY COUNTIES, GEORGIA

High School	Number		Per Cent Completed Tests
	Enrolled	Completed Tests	
Murray	491	402	81 9
North Whitfield	537	486	90 5
Valley Point	396	375	94 7
Westside	222	192	86 5
Dalton	651	559	85 9
Total white	2297	2014	87 7
Emory (Negro)	121	98	81 0
Total all students	2418	2112	87 3

†Includes one student not tested with histoplasmin

tests were given in one forearm, and one in the other, by intracutaneous injection of 0 1 ml The products used for the survey were histoplasmin H-42 prepared by Dr Arden Howell, Jr of the Public Health Service, coccidioidin C-24, prepared by Dr Charles E Smith of the University of California, and tuberculin PPD-S, the international standard PPD, prepared by Dr Florence Seibert of the Henry Phipps Institute For study purposes, the histoplasmin was used in two dilutions, the standard 1 100 dilution and a 1 50 dilution, given alternately as the students came to be tested Coccidioidin 1 100 dilution and the 5 TU (0 0001 mg) dose of PPD-S were given to all students All products were labelled in code on the bottles and the members of the testing team were not told what the bottles contained

Reactions were read in 48 (or 72) hours by measuring and recording the transverse diameter of palpable induration All readings (except in Emory High) were done by one experienced nurse

Photofluorograms of the chest were taken at the time of the skin testing by a mobile unit provided by the Georgia Department of Public Health, through the courtesy of Dr Clara Barrett The films were read independently by two Public Health Service physicians who had no knowledge of the skin test results and who simply interpreted the films as normal or as showing evidence of calcification (definite or possible), infiltration, other (non-tuberculous) pathology or a combination of findings

History of all places of residence since birth was also obtained for each student by direct questioning at the time of the testing

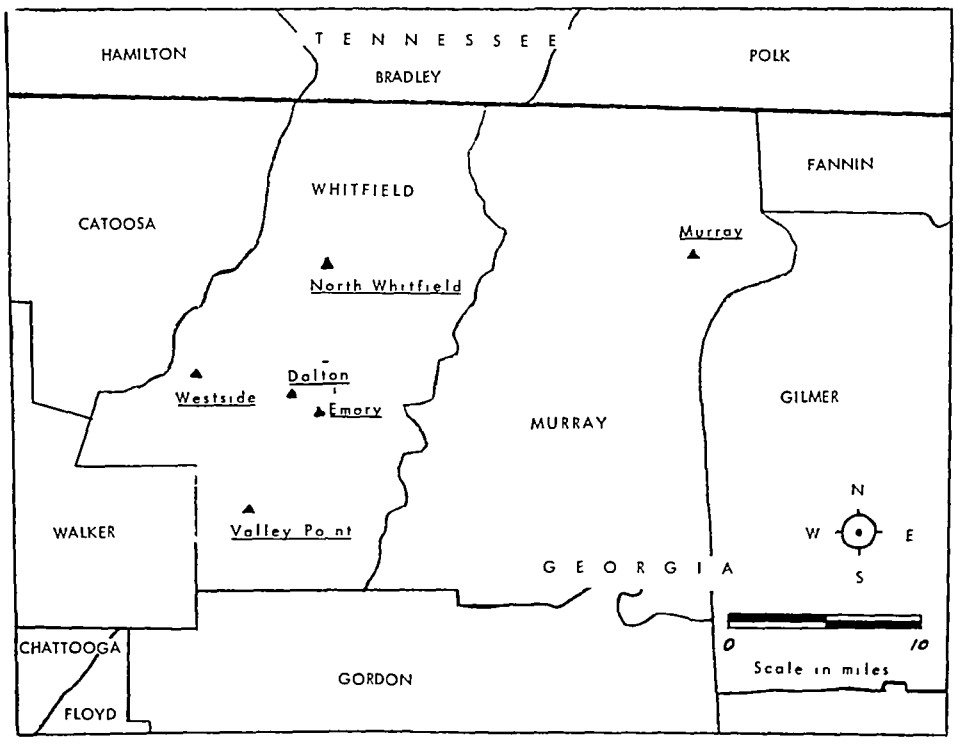


FIGURE 1 Map of Whitfield and Murray Counties, Georgia, showing location of the six public high schools and the adjoining counties

TABLE II

NUMBER AND PER CENT OF STUDENTS WITH TUBERCULIN REACTIONS OF 10 MM OR MORE, AMONG 14-16 AND 17-19 YEAR AGE GROUPS, BY SCHOOL AND SEX, ACCORDING TO RESIDENCE IN WHITFIELD-MURRAY COUNTIES, GEORGIA

	Lifetime and Non-Lifetime Residence									Lifetime Residence		
	All Ages			14-16 Years			17-19 Years			All Ages		
		Reactions 10 Mm or More			Reactions 10 Mm or More			Reactions 10 Mm or More			Reactions 10 Mm or More	
School and Sex	No Tested	No	Per Cent	No Tested	No	Per Cent	No Tested	No	Per Cent	No Tested	No	Per Cent
Murray	402	19	4 7	213	11	5 2	189	8	4 2	336	16	4 8
North Whitfield	486	25	5 1	287	11	3 8	199	14	7 0	359	16	4 5
Valley Point	375	15	4 0	264	12	4 5	111	3	2 7	290	12	4 1
Westside	192	6	3 1	131	5	3 8	61	1	1 6	134	4	3 0
Dalton	559	30	5 4	286	11	3 8	273	19	7 0	344	18	5 2
Total white students	2014	95	4 7	1181	50	4 2	833	45	5 4	1163	66	4 5
Male	929	45	4 8	530	25	4 7	399	20	5 0	663	31	4 7
Female	1085	50	4 6	651	25	3 8	434	25	5 8	800	35	4 4
Emory (Negro)	98	18	18 4	63	12	19 0	35	6	17 1	79	17	21 5

Results

Tuberculin sensitivity

The frequency distribution by size of reactions to the 5 TU dose of PPD is given in figure 2, where the horizontal axis shows the diameter of induration (in 2 mm groups) and the vertical axis shows the percentage of reactions of each specified size More than 75 per cent of the tuberculin reactions were recorded as 0 or 1 mm, about 12 per cent as 2 or 3 mm and about 3 per cent as 4 or 5 mm For reactions of 6 to 25 mm, the frequencies were very low and nearly the same for each 2 mm grouping but with a slight indication of a peak at 14-17 mm There is no clear-cut separation of the distribution into two groups The very large reactions, which can be presumed to represent tuberculous infection, merge with the very small reactions, which are undoubtedly negative

Interpretation of the tuberculin reactions in the present study may, however, be based on material from other reports [10 12] Many of the reactions measuring less than 10 mm to the 5 TU test, and this is particularly true in the southeastern part of the country, apparently represent nonspecific (heterologous) sensitivity Reactions in the range from about 3 or 4 to perhaps 9 mm represent a mixture of positive, negative and

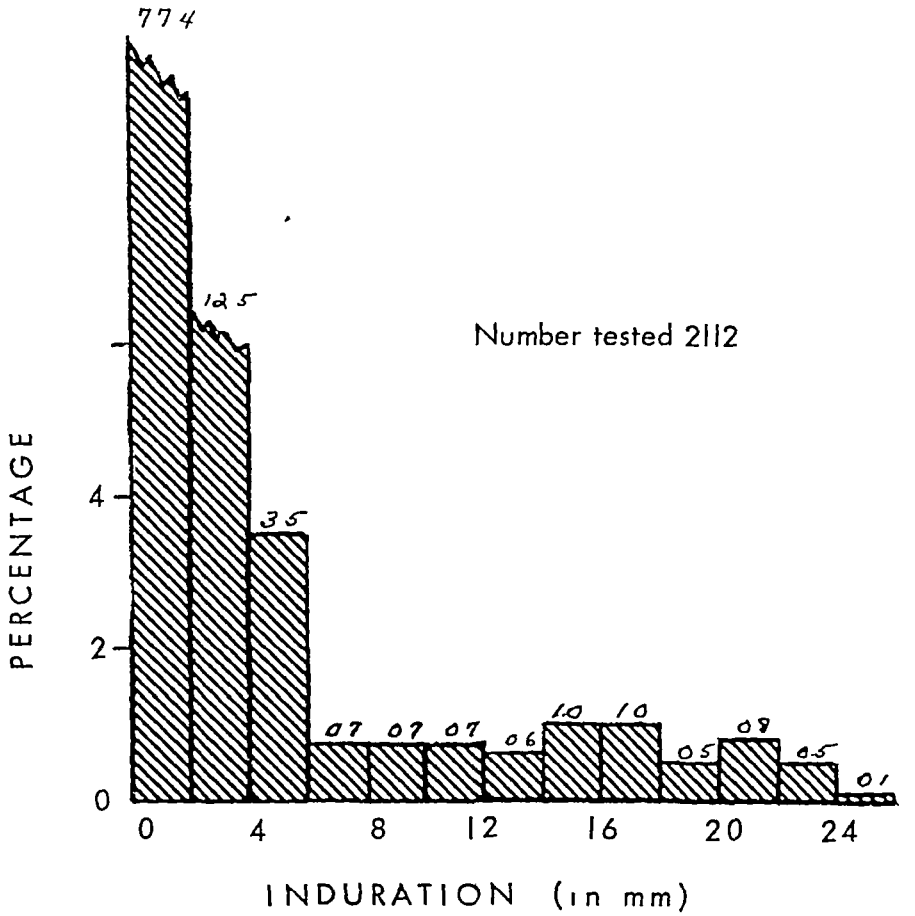


FIGURE 2 Frequency distribution by size of reaction to 5 TU of PPD-S, among high school students in Whitfield-Murray Counties, Georgia

nonspecific reactions Thus, as indicated in a recent publication,[11] a fair estimate of the prevalence of tuberculous infection can be made by using a criterion of 10 mm or more for a positive reaction

The percentage of positive tuberculin reactors, so defined, is given in table 2 by school (and sex) according to residence and age Lifetime residents of the community include only those persons who were born in, and had never lived outside of, Whitfield or Murray Counties or any of the 10 adjoining counties (see map, fig 1) Almost three-fourths of the students, 1,542 of the 2,112, could be classified as lifetime residents The average percentage of tuberculin reactors among the white students was low, less than 5 per cent, with only minor variations from school to school and by sex, age and residence in the community

The prevalence of infection among Negro students, although less than 100 were tested, appears to be several times higher than among white students

Histoplasmin sensitivity

Reactions to histoplasmin are distributed according to size in figure 3 About 60 per cent of the reactions were recorded as 0 or 1 mm, followed by an abrupt drop to 6 5 per cent for reactions of 2 or 3 mm, 1 4 per cent for 4 or 5 mm, and only 1 1 per cent for reactions of 6 or 7 mm Thereafter, with increasing size of reaction, the frequencies rose to reach a maximum of 7 1 per cent at 12-15 mm and then tapered off The distribution is bimodal in form, with the right-hand segment resembling the normal probability frequency curve and separating itself from the

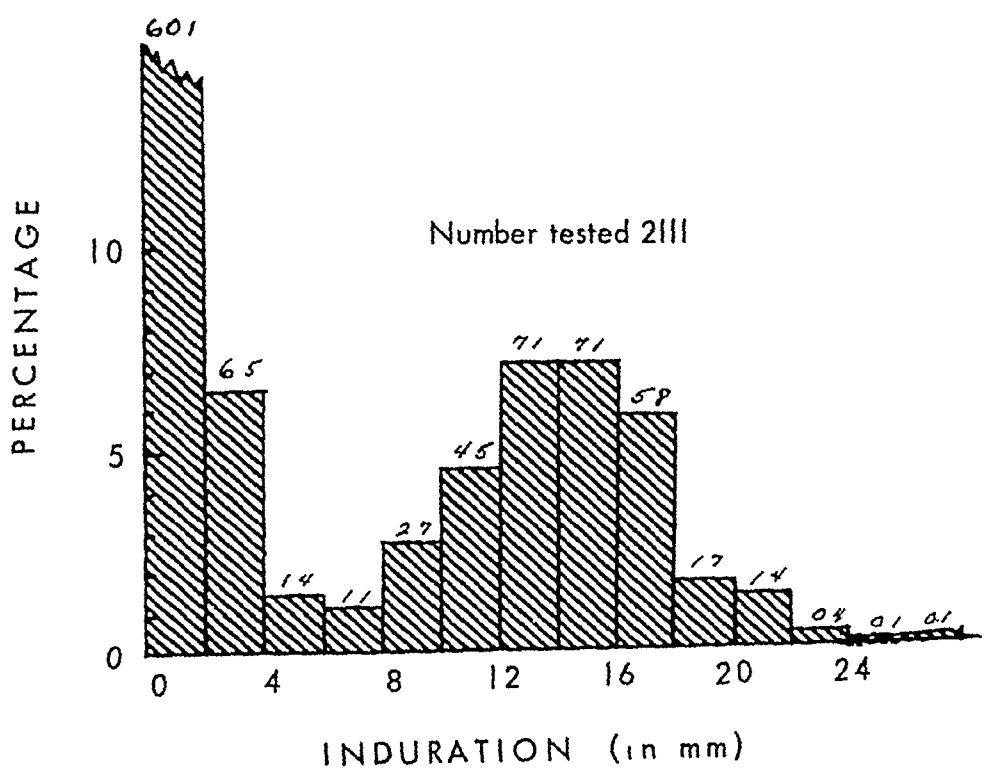


FIGURE 3 Frequency distribution by size of reaction to histoplasmin (H-42), among high school students in Whitfield-Murray Counties, Georgia

left-hand segment in the neighborhood of 6 mm As the two doses of histoplasmin used in the present study produced only small differences in the sizes of the reactions,[14] results for both doses have been combined

From the form of the distribution, it may be inferred that most of the reactions measuring less than 6 mm belong to the negative (uninfected) group and most of the larger reactions belong to the positive (infected) group The two groups overlap to some degree in the range of about 4 to 9 mm

The percentage of students with positive histoplasmin reactions (6 mm or more) is given in table 3 for each school and, within each school, by sex, age group and residence in the community For students in the four rural schools, the frequency of positive reactors ranged from about 19 to 25 per cent, with an average of nearly 22 per cent The frequencies were more than twice as high for students attending the two urban schools in Dalton—55 per cent for the white students at Dalton High and 56 per cent for the Negro students at Emory High

In almost all instances, somewhat higher frequencies of positive reactors were found among boys than girls, among older than younger students within the six-year age span, and for lifetime as compared with non-lifetime residents The apparent reversal in the frequency with age among

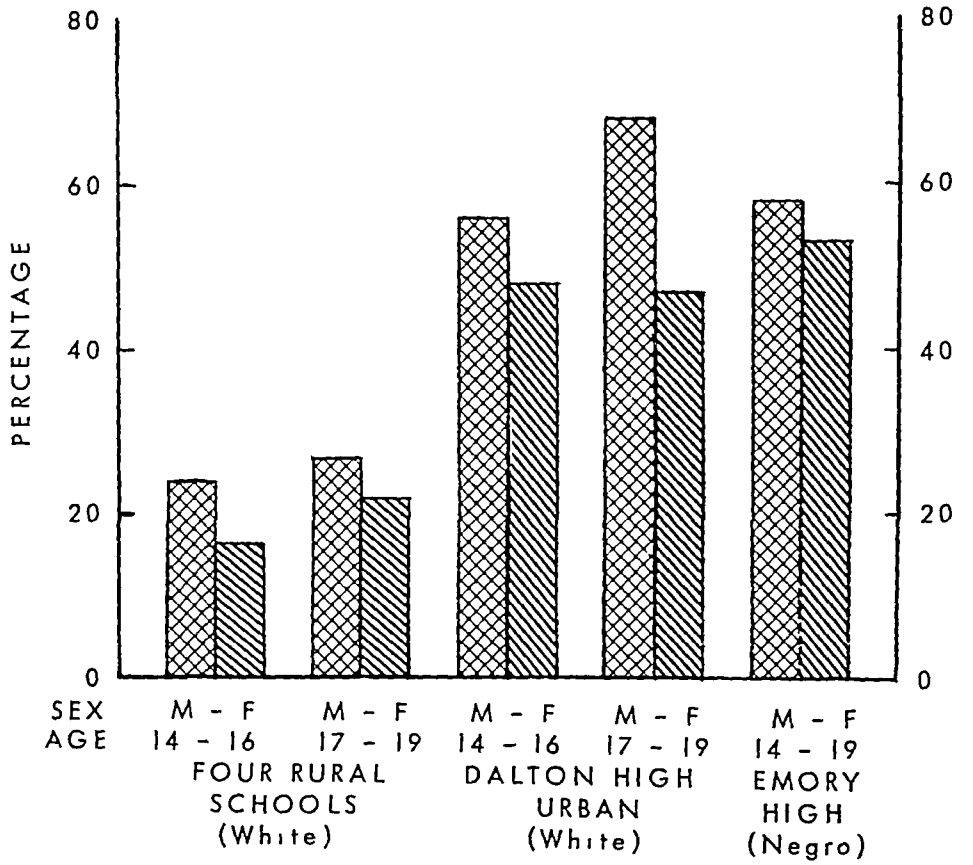


FIGURE 4 Percentage of histoplasmin reactions 6 mm or more among high school students grouped according to age, sex, race, and rural or urban residence in Whitfield-Murray Counties, Georgia

TABLE III

NUMBER AND PER CENT OF STUDENTS WITH HISTOPLASMIN REACTIONS OF 6 MM OR MORE, AMONG 14-16 AND 17-19 YEAR AGE GROUPS, BY SCHOOL AND SEX, ACCORDING TO RESIDENCE IN WHITFIELD-MURRAY COUNTIES, GEORGIA

School and Sex	Lifetime and Non-Lifetime Residence									Lifetime Residence		
	All Ages			14-16 Years			17-19 Years			All Ages		
		Reactions 6 Mm or More			Reactions 6 Mm or More			Reactions 6 Mm or More			Reactions 6 Mm or More	
	No Tested	No	Per Cent	No Tested	No	Per Cent	No Tested	No	Per Cent	No Tested	No	Per Cent
MURRAY	401	77	19 2	212	33	15 6	189	44	23 3	335	64	19 1
Male	177	34	19 2	93	16	17 2	84	18	21 4	147	29	19 7
Female	224	43	19 2	119	17	14 3	105	26	24 8	188	35	18 6
NORTH WHITFIELD	486	109	22 4	287	60	20 9	199	49	24 6	359	73	20 3
Male	214	66	30 8	117	38	32 5	97	28	28 9	155	47	30 3
Female	272	43	15 8	170	22	12 9	102	21	20 6	204	26	12 7
VALLEY POINT	375	81	21 6	264	52	19 7	111	29	26 1	290	63	21 7
Male	166	42	25 3	125	28	22 4	41	14	34 1	123	34	27 6
Female	209	39	18 7	139	24	17 3	70	15	21 4	167	29	17 4
WESTSIDE	192	48	25 0	131	33	25 2	61	15	24 6	134	35	26 1
Male	87	21	24 1	54	12	22 2	33	9	27 3	66	16	24 2
Female	105	27	25 7	77	21	27 3	28	6	21 4	68	19	27 9
TOTAL (White Rural)	1,454	315	21 7	894	178	19 9	560	137	24 5	1 118	235	21 0
Male	644	163	25 3	389	94	24 2	255	69	27 1	191	126	25 7
Female	810	152	18 8	505	84	16 6	305	68	22 3	627	109	17 4
DALTON (White Urban)	559	308	55 1	285	149	52 3	273	159	58 2	311	202	58 7
Male	284	177	62 3	140	79	56 4	144	98	68 1	171	113	66 1
Female	275	131	47 6	145	70	48 3	129	61	47 3	173	89	51 4
EMORY (Negro)	98	55	56 1	63	40	63 5	35	15	42 9	79	47	59 5
Male	51	30	58 8	27	19	70 4	24	11	45 8	43	27	62 8
Female	47	25	53 2	36	21	58 3	11	4	36 4	36	20	55 6

Negro students may be ascribed to random variations in a small sample

Figure 4 presents a summary picture of the histoplasmin test results The high frequencies of positive reactors in the two urban schools are contrasted with the much lower frequencies in the four rural schools The figure brings out the slightly higher proportion of reactors among boys than girls—a finding consistent with reports from other communities [1 6 16, 17]

Coccidioidin sensitivity

Coccidioidomycosis has not been reported, so far as we know, in a native resident of northwestern Georgia, and studies of coccidioidin sen-

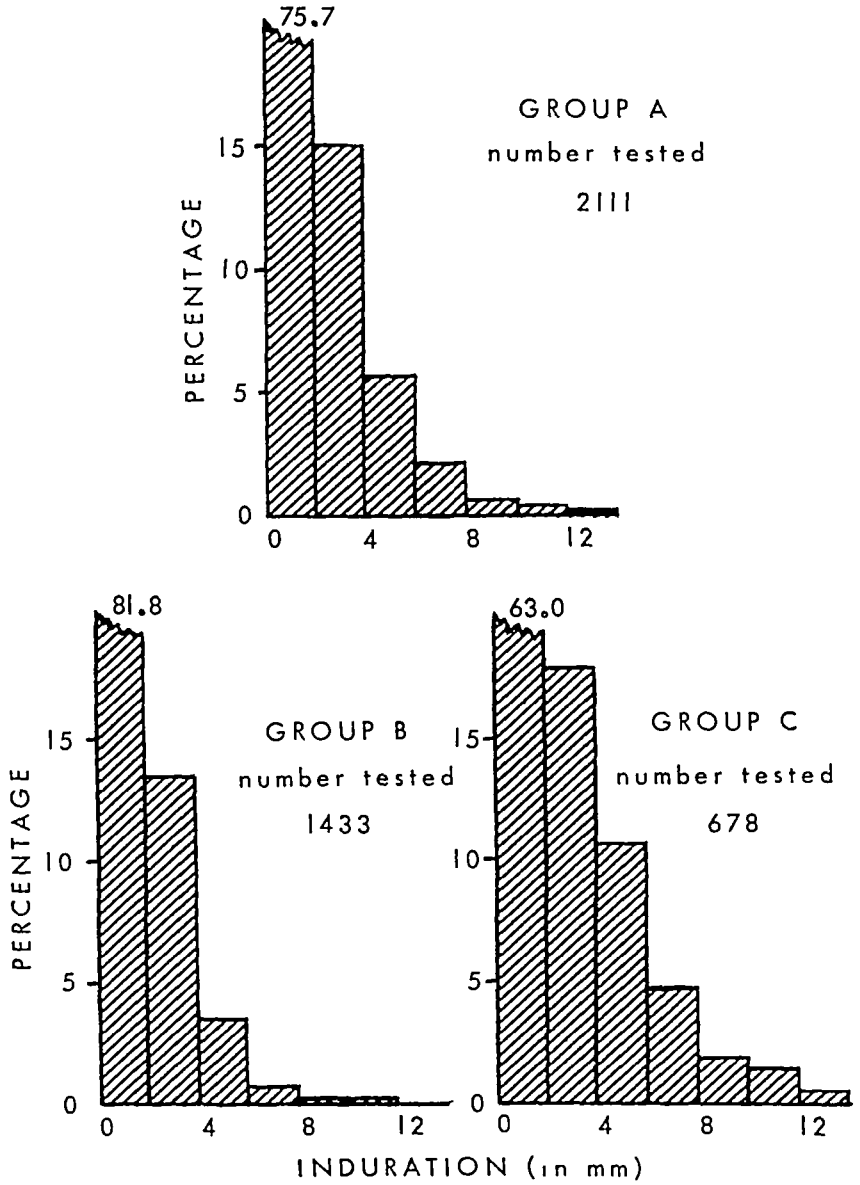


FIGURE 5 Frequency distribution by size of reaction to coccidioidin (C-24) among all high school students (A), those with a histoplasmin reaction of less than 6 mm (B) and those with a histoplasmin reaction of 6 mm or more (C) in Whitfield-Murray Counties, Georgia

sitivity indicate that the endemic area of Coccidioides infection in the United States is limited to the southwest [5, 10] The present survey thus offered an opportunity to study the nature and frequency of nonspecific (heterologous) sensitivity to coccidioidin in a locality far from the Coccidioides endemic area

The frequency distribution by size of reaction to coccidioidin is given in the upper part of figure 5 for the entire study population and, in the lower section, for those with histoplasmin reactions of less than 6 mm (left) and those with histoplasmin reactions of 6 mm or more (right) The distribution for the total group shows that all but a very few of the reactions were recorded as zero or only a few millimeters in diameter the frequency of reactions 6 mm or more was 3 4 per cent

Because of the clear point of separation at 6 mm for histoplasmin reactions (see fig. 3), students with reactions of less than 6 mm probably represent a fairly "pure" group of persons not infected with histoplasma Coccidioidin reactions in this group, shown in the lower left section of figure 5, can not be regarded as cross-reactions owing to histoplasmal infection They must, with few exceptions (discussed below), represent the kind of reactions that can be expected in a group free of infection with coccidioides and histoplasma Only 1 per cent of the reactions measure more than 5 mm and only 0 2 per cent measure more than 7 mm

The distribution of coccidioidin reactions for the group of students who probably have been infected with histoplasma, shown in the lower right section of the figure, provides information about the size and frequency of nonspecific (cross) reactions to coccidioidin in persons sensitized by histoplasma infection Comparison of this distribution with the one at the left indicates that at least some of the 2 and 3 mm reactions must be cross reactions, and a substantial proportion of the 4 and 5 mm reactions and almost all of the reactions of 6 mm or more must be cross reactions

Although the details are not given, results for boys and girls were analyzed separately Among the 370 boys with positive reactions (6 mm or more) to histoplasmin, coccidioidin reactions of 4 mm or more were found in 85 (23 0 per cent), as compared with 45 of the 309 girls (14 6 per cent) A difference between the sexes was also found for students with negative reactions (less than 6 mm) to histoplasmin for boys the frequency of coccidioidin reactions of 4 mm or more was 6 4 per cent (39 out of 609), for girls it was 3 3 per cent (27 out of 824) In both instances the differences are statistically significant

As shown in table 4, 16 of the students had coccidioidin reactions of 10 mm or more The two with the largest reactions (17 mm and 20 mm) had lived in the southwest and probably acquired an infection with Coccidioides A few others may also have lived in the southwest but forgot to say so when asked for their residence history, or they may have merely visited or lived for a short period in the coccidioides endemic area, a fact that would not have been brought out in obtaining the resi-

dence history But the remainder may simply be highly sensitive persons with fairly strong cross-reactions, as in all but 2 instances the reactions to coccidioidin were smaller than to histoplasmin

There is no evidence from this material that Coccidioides infection is indigenous to northwestern Georgia

X-ray findings

The 70 mm x-ray films for 87 of the 2,111 students were interpreted independently by two readers as showing either pulmonary calcification or infiltration In 73 instances both readings indicated the presence of calcifications, in 12 instances one indicated calcification and the other an infiltration, and in 2 instances both readings agreed on the presence of an infiltration

All but six of the 87 students with pulmonary findings reacted to histoplasmin, as shown in table 5 Only three of the 87 reacted to tuberculin, 2 of whom were histoplasmin non-reactors, the third had a histoplasmin reaction of 17 mm Two had coccidioidin reactions measuring 11 mm and both of them had histoplasmin reactions of 15 mm As both were lifetime residents of the community, having been born and lived all their

TABLE IV

CORRELATION OF SIZES OF REACTIONS TO HISTOPLASMIN AND COCCIDIOIDIN AMONG HIGH SCHOOL STUDENTS IN WHITFIELD-MURRAY COUNTIES, GEORGIA

Reaction to Histoplasmin in millimeters of induration	Reaction to Coccidioidin in millimeters of induration								
	0-1	2-3	4-5	6-7	8-9	10-11	12-13	14 or More	Total
0 - 1	1047	160	45	10	1	2		1 (17)†	1266
2 - 3	100	32	4	2					138
4 - 5	25	3	1						29
6 - 7	14	4	4	1					23
8 - 9	47	8	1	1				1 (20)‡	58
10 - 11	60	20	11	2	1	1			95
12 - 13	92	30	13	8	6	1			150
14 - 15	87	28	22	5	2	5	1		150
16 - 17	77	17	15	7	3	2	1		122
18 - 19	28	4	2	2					36
20 - 21	11	9	3	6	1				30
22 - 23	7	1	1						9
24 - 25	2					1			3
26 - 27	2								2
Total	1599	316	122	44	14	12	2	2	2111

† 5 years residence in California
‡ 2 years residence in Texas

lives in Whitfield County, their reactions to coccidioidin were probably nonspecific and the pulmonary calcifications a result of histoplasma infection

Analysis of the frequency of calcifications among histoplasmin reactors of 6 mm or more revealed an unexpected statistically significant difference between the sexes the calcification rate was 15 1 per cent among boys and only 8 1 per cent among girls

Thus, the pulmonary findings can be attributed to histoplasmosis in all but seven of the 87 instances In two of those seven cases the findings can probably be ascribed to tuberculosis and in both instances the two readers identified the same lesions, described as infiltrations in the right upper lung field In one other case the student reacted to both tuberculin and histoplasmin, so the findings could be due to either infection And in the four remaining cases, the etiology of the lesion is unknown, as the students did not react to any of the three skin tests

TABLE V

FREQUENCY OF PULMONARY CALCIFICATIONS, INFILTRATIONS BY SIZE OF REACTION TO HISTOPLASMIN, AMONG HIGH SCHOOL STUDENTS IN WHITFIELD-MURRAY COUNTIES, GEORGIA

Histoplasmin Reaction (Millimeters)	Total		Calc /Infilt *	
	Number	Per Cent	Number	Per Cent
0 - 1	1266	60 1	6**	0 5
2 - 3	138	6 5		
4 - 5	29	1 4		
6 - 7	23	1 1	4	9 9
8 - 9	58	2 7	4	
10 - 11	95	4 5	9	14 7
12 - 13	150	7 1	27	
14 - 15	150	7 1	19†	11 4
16 --17	122	5 8	12‡	
18 - 19	36	1 7	4	7 5
20 - 21	30	1 4	2	
22 - 23	9	0 4		
24 - 25	3	0 1		
26 - 27	2	0 1		
Total	2111	100 0	87	4 1
Reactions less than 6 mm	1433	67 9	6	0 4
Reactions 6 mm or more	678	32 1	81	11 9

*Two readers read the 70 mm films independently as showing calcification or infiltration
**Includes 2 persons with tuberculin reactions of 20 mm and 21 mm
†Includes 2 persons with coccidioidin reactions of 11 mm (both lifetime residents of Whitfield County)
‡Includes 1 person with a tuberculin reaction of 18 mm

Discussion

A striking finding in the present survey is the reversal of the usual urban-rural relation in prevalence of histoplasmin sensitivity Prior and Allen[15] reported some 10 years ago that the histoplasmin reactor rate among Ohio University students was appreciably higher for those coming from farms than from cities, and later reports from other areas[3, 5, 16] have been in substantial agreement with their findings The most recent contribution to the subject, a study by Furcolow and Ney[20] of Kansas City school children, has led those authors to conclude that there is "a strong positive relationship between amount of contact with farms and the prevalence of positive histoplasmin skin tests"

In the present survey the high frequency of histoplasmin reactors in students attending the two urban schools and the much lower frequency of reactors in the four rural schools points directly to a source of infection within the urban area of Dalton to which both Negro and white children appear to be exposed about equally We would postulate further that contact with a source in Dalton could account for many, if not most, of the histoplasmin reactors found among the rural residents This indication of a potent source of infection in an urban rather than rural area is of considerable epidemiological interest, as it may represent a unique situation which in no way invalidates the evidence that sources of infection are ordinarily found in rural areas

Analysis of the sizes of the histoplasmin reactions in the present material, as compared with the sizes of reactions found in other areas where Coccidioides and other fungi cause nonspecific (heterologous) sensitization to histoplasmin,[19, 21, 22] indicates that histoplasmin sensitivity in the Whitfield-Murray area is specific for infection with histoplasma The high correlation between pulmonary calcification and histoplasmin sensitivity further supports that interpretation It also suggests that the source of infection in the community has been present for some years, as it takes several years for calcium to replace a pulmonary infiltration

Most of the coccidioidin sensitivity in lifetime residents of the area is interpreted as nonspecific The coccidioidin reactions were of small average size and were generally found in persons who reacted to histoplasmin There was, however, a significantly higher frequency of nonspecific coccidioidin reactions in boys than in girls As far as we know, this is a new and unexpected finding, further study of it should lead to a better understanding of the nature and significance of nonspecific sensitivity to the fungus antigens

Tuberculin sensitivity showed a frequency of about 5 per cent in the white high school students—a prevalence only slightly higher than that reported for young people in various other communities[1, 2, 5, 7, 9] An average prevalence of 5 per cent at 16 to 17 years of age corresponds to an average infection rate of a little more than 3 per 1,000 per year If, as seems likely, the infection rate has dropped in this community, as it has in most communities, during the lifetime of these young people, many

of them probably got their tuberculous infection in early childhood In other words, the infection rate at the present time may be considerably lower than 3 per 1,000 per year

From a medical and public health standpoint, the present survey reveals that there may be four or five students in the high school age population who have had a coccidioidal infection, somewhat more than 100 who have had a tuberculous infection and at least 700 who have had a histoplasmal infection Clearly, histoplasmosis is an infection to be reckoned with in this community Abnormalities in the chest x-ray films of these young persons are far more often a result of histoplasmal than tuberculous infection

As an immediate consequence of the survey, a systematic search has been started through the Health Department's tuberculosis case register for persons with histoplasmosis misdiagnosed as tuberculosis Skin testing with histoplasmin in addition to tuberculin has also been instituted in the clinic work Tuberculosis is of course still the main problem, but the frequency of tuberculin reactors among the high school students indicates that the infection rate has been relatively low during the last 15 years and an energetic campaign to find and eliminate the infectious cases in the community should result in a further reduction in the rates

SUMMARY

A skin-testing survey with histoplasmin, coccidioidin and tuberculin, supplemented with 70 mm chest photofluorograms, was carried out among students attending the six public high schools in Whitfield and Murray Counties, Georgia About 90 per cent of the total estimated enrollment of 2,400 participated in the survey

Results showed a striking reversal of the usual rural-urban pattern of prevalence of sensitivity to histoplasmin Students living in the urban area of Dalton had a reactor rate of 55 per cent as compared with a rate of 22 per cent for those living in the rural areas Pulmonary calcifications were found in about 12 per cent of the histoplasmin reactors Analysis of the findings lead directly to the hypothesis that there is a source of histoplasma infection within the City of Dalton which has been present for at least several years

About 5 per cent of the white students had reactions interpreted as positive to the 5 TU test with PPD, with only small variations around that average from school to school and between boys and girls The rates were slightly higher for the older as compared with the younger students within the six-year age span 14 to 19 years

Coccidioidin reactions, which were of small average size, were interpreted as nonspecific (or cross) reactions owing to histoplasma infection

RESUMEN

Se llevó a cabo una investigación con las pruebas cutáneas de histoplasmina, coccidioidina y tuberculina entre los estudiantes de seis escuelas

secundarias publicas completándose con fotofluorografias de 70 mm en los condados de Whitfield y Murray en Georgia

Aproximadamente 90 por ciento del total de los 2,400 estudiantes participaron en la investigación

Los resultados demostraron una notable inversión de la prevalencia de sensibilidad de la tuberculina en comparación con la habitual relación de la población urbana a la rural

Los estudiantes que viven en el área urbana de Dalton, tienen una proporción de reactores de 55 por ciento comparada con un 22 por ciento de los que viven en el área rural

Se encontraron calcificaciones como en 12 por ciento de los reactores a la histoplasmina El análisis de los resultados condujo a la hipótesis de que existe una fuente de infección de histoplasma dentro de la ciudad de Dalton que ha estado ahí por lo menos varios años

Aproximadamente 5 por ciento de los estudiantes de raza blanca tuvieron reacciones positivas a 5 TU con PPD con sólo pequeñas variantes entre las diversas escuelas y entre muchachos y señoritas Las proporciones fueron ligeramente mayores para los de más edad comparándose con los menores dentro del término de seis años entre los 14 y 19 años

Las reacciones a la coccidioidina, que en general fueron de tamaño pequeño se interpretaron como no específicas debidas a la infección de histoplasmosis

RESUME

Un contrôle des réactions cutanées à l'histoplasmine, à la coccidioidine et à la tuberculine, associé à des radiophotographies du thorax de 70 mm fut pratiqué chez les étudiants fréquentant les six facultés publiques des Comtés de Whitfield et Murray, en Géorgie Environ 90% de l'effectif total que avait été estimé à 2 400 participèrent au contrôle

Les résultats montrèrent un contraste frappant entre les tracés habituels rural et urbain de la sensibilité à l'histoplasmine Chez les étudiants vivant dans la zone urbaine de Dalton, on constata un taux de réaction de 55%, alors que le taux de ceux qui vivent dans les zones rurales était de 22% Des calcifications pulmonaires furent trouvées chez 12% des individus réagissant à l histoplasmine L'analyse de ces constatations entraine directement à l'hypothèse qu'il y a une source d'infection qui existe depuis au moins quelques ans dans la cité de Dalton

Environ 5% des étudiants de race blanche fournirent des réactions interprétées comme positives à 5 unités de tuberculine P P D , avec seulement de légères variations d'une école a l'autre et selon que l'on s'adresse aux garçons ou aux filles Les taux furent légèrement plus élevés pour les étudiants les plus agés, la comparaison portant sur les étudiants dont l'âge variait de 14 à 19 ans

Les réactions à la coccidioidine de dimension généralement réduite, furent interprétées comme non spécifiques, compte tenu de l'infection par l'histoplasma

ZUSAMMENFASSUNG

Eine Untersuchungsreihe mit Hautempfindlichkeitspruefungen auf Histoplasmin Coccidioidin und Tuberkulin, ergaenzt durch 70 mm Thorax-Schirmbilder, wurde unter den Schulern durchgefuehrt, die sechs Staatlichen hoheren Lehranstalten in den Kreisen Whitefield und Murray im Staate Georgia angehoerten Ungefahr 90% der gesamten auf 2400 berechneten Angehoerigen nahmen an der Untersuchung teil

Die Ergebnisse zeigten eine auffallende Umkehr der gewohnlichen Verhaltnisse von Land zu Stadt bei dem Auftreten der Histoplasminempfindlichkeit, Schuler, die im stadtischen Bereich von Dalton lebten, hatten einen Prozentsatz von 55% positiven Reaktionen im Verhaltnis zu einer Zahl von 22% bei denjenigen, die auf dem Lande lebten Pulmonale Verkalkungen wurden in ungefahr 12% der auf Histoplasmin reagierenden Personen gefunden Eine Auswertung der Befunde fuhrte unmittelbar zu der Hypothese, dass in der Stadt Dalton eine Quelle fur eine Infektion mit Histoplasma besteht, die seit mindestens mehreren Jahren existiert

Ungefahr 5% der weissen Schuler hatten Reaktionen, die als positiv bei dem Test mit 5 Tuberkulineinheiten mit PPD gedeutet wurden und mit nur geringen Abweichungen von diesem Durchschnitt von Schule zu Schule und zwischen Knaben und Madchen Die Zahlen lagen ein wenig hoher bei den alteren im Vergleich zu den jungeren Schulern innerhalb der 6-Jahres-Spanne von 14 19 Jahren

Coccidioidin-Reaktionen, die durchschnittlich von geringer Grosse waren, wurden als unspezifische (oder Kreuz-) Reaktionen gedeutet infolge Infektion mit Histoplasma

REFERENCES

1 Furcolow, M L, Schwarz, J, Hewell, B A and Grayston, J T "Incidence of Tuberculin, Histoplasmin, and Blastomycin Reactors Among a Group of School Children," *Am J Public Health*, 43 1523, 1953

2 Jordan, K B and Jordan, L S "County Wide Tuberculin Testing," *Dis Chest*, 26 528, 1954

3 Grayston, J T, Heeren, R H and Furcolow, M L "The Geographic Distribution of Histoplasmin Reactors Among School Age Children Within a Rural Iowa County," *Am J Hyg*, 62 201, 1955

4 Myers, J A, Gunlaugson, F G, Meyerding, E A and Roberts, J "Importance of Tuberculin Testing of School Children—A Twenty-Eight Year Study," *J A M A*, 159 185, 1955

5 Sachs, D, Smith, R T, Fleming, D S and Furcolow, M L "The Prevalance of Positive Reactions to Tuberculin and Histoplasmin in a Rural Minnesota County," *Am J Hyg*, 62 43, 1955

6 Furcolow, M L Federspiel, C F and Larsh, H W "Histoplasmin, Coccidioidin, and Tuberculin Sensitivity Among School Children in Two Texas Counties," *Public Health Rep*, 70 12, 1955

7 Furcolow, M L "On the Usefulness of the Tuberculin Skin Test," *Am J Public Health*, 46 1064, 1956

8 Harris, J S, Smith, J G, Humbert, W C, Conant, N F and Smith, D T "North American Blastomycosis in an Epidemic Area," *Public Health Rep*, 72 95, 1957

9 Edwards, L B, Peeples, W J and Berger, A G "Prevalence of Sensitivity to Tuberculin and Histoplasmin Among High School Students in Montgomery County, Maryland," *Pediatrics*, 21 389, 1958

10 Palmer, C E "Tuberculin Sensitivity and Contact with Tuberculosis Further Evidence of Nonspecific Sensitivity," *Am Rev Tuberc*, 68 678, 1953

11 Palmer, C E, Krohn, E F, Manos, N E and Edwards, L B "Tuberculin Sensitivity of Young Adults in the United States," *Public Health Rep*, 71 633, 1956

12 Edwards, L B and Krohn, E F "Skin Sensitivity to Antigens Made From Various Acid-Fast Bacteria," *Am J Hyg*, 66 253, 1957

13 Edwards, L B and Palmer, C E "Epidemiologic Studies of Tuberculin Sensitivity I Preliminary Results with Purified Protein Derivatives Prepared from Atypical Acid-fast Organisms," *Am J Hyg*, 1958 (in press)

14 Palmer, C E and Edwards, P Q "The Dose of Histoplasmin H-42 for Skin Testing," *Am Rev Tuberc*, 77 546, 1958

15 Prior, J A and Allen, M F "Geographic Distribution of Histoplasmin and Tuberculin Reactors Among Ohio State University Freshmen and Student Nurses Training in Columbus, Ohio Hospitals," *Pub Health Reports*, 62 1608, 1947

16 Furcolow, M L and Sitterly, J "Further Studies of the Geography of Histoplasmin Sensitivity in Kansas and Missouri," *J Kansas Med Soc*, 52 584, 1951

17 Beadenkopf, W G, Loosli, C G, Lack, H, Rice, F A and Slattery, R V "Tuberculin, Coccidioidin, and Histoplasmin Sensitivity in Relation to Pulmonary Calcifications A Survey Among 6,000 Students at the University of Chicago," *Public Health Rep*, 64 17, 1949

18 Smith, C E "Diagnosis of Pulmonary Coccidioidal Infections," *California Med*, 75 385, 1951

19 Edwards, P Q and Palmer, C E "Prevalence of Sensitivity to Coccidioidin, with Special Reference to Specific and Nonspecific Reactions to Coccidioidin and to Histoplasmin," *Dis Chest*, 31 35, 1957

20 Furcolow, M L and Ney, P E "Epidemiologic Aspects of Histoplasmosis," *Am J Hyg*, 65 264, 1957

21 Palmer, C E, Edwards, P Q and Allfather, W E "Characteristics of Skin Reactions to Coccidioidin and Histoplasmin, with Evidence of an Unidentified Source of Sensitization," *Am J Hyg*, 66 196, 1957

21 Edwards, P Q "Histoplasmin Testing in Different Geographic Areas," *Lancet*, 2 707, 1957

Pulmonary Resection for Tuberculosis Under Protection of Viomycin, Promizole and Pyrazinamide

WATTS R WEBB, M D, F C C P** and KONSTANTIN SPARKUHL, M D
Jackson, Mississippi

Introduction

The addition of chemotherapeutic agents to the armamentarium for the treatment of tuberculosis has been of inestimable value in decreasing morbidity and mortality It has been largely responsible for the great progress in resectional pulmonary surgery, which otherwise usually would have been denied the patient As is well known, however, bacterial resistance to the antimicrobial drugs has developed in a sizable tuberculous population and this may present an ever-increasing problem in the future treatment and retreatment of tuberculosis Unless proper use of specific drug combinations is effected at all times to meet the particular problem at hand, the effectiveness of the drugs will be lost in a significant percentage of cases Many workers are making great strides toward preventing resistance by application of carefully selected treatment schedules and well-timed definitive surgery

At present, a large backlog of patients is developing with open positive lesions harboring tubercle bacilli either proved or presumptively resistant to PAS, INAH and streptomycin These are posing a special problem and require most thoughtful handling by the specialist team

Many reports now attest to the increased percentage of complications that occur whenever resection is attempted in the presence of tubercle bacilli resistant to the antimicrobial therapy Coleman and Bunch[1] early pointed out the increased incidence of major complications, especially bronchopleural fistulae, following surgery in patients with streptomycin resistant strains Murphy[2] reported satisfactory results in only 77 6 per cent of operations for cavitary lesions as compared to 94 7 per cent where closed lesions had been resected Where sputa were positive, only 82 8 per cent of the patients had good results as compared with 94 4 per cent when the sputa were negative

Holland, Bell and Welles[3] found similar results in 75 patients with open positive lesions Of an original chemotherapy susceptible group, there was only one major complication in 19 resections as contrasted with five complications in nine resections in the presence of bacterial resistance The retreatment group had three major complications in 22 resections if the bacilli were susceptible, but with resistant organisms there were nine major complications in 33 resections Overall favorable results were achieved in

*Read by title at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957

**From the Departments of Surgery, Mississippi State Sanatorium and University of Mississippi Medical Center

95 5 per cent of the susceptible group but in only 71 per cent of the resistant group They found that late tuberculous complications occurred in one-third of their resistant cases, a morbidity reminiscent of the predrug era Of their total 17 cases with postoperative parenchymal reactivation in over 500 resections, 15 had resistant tubercle bacilli In eight patients in whom resistance was not suspected, parenchymal reactivation followed promptly after segmental excision As a result, they prefer to do lobectomies rather than segmental resections in the presence of resistance

Lees,[4] in reviewing more than 300 resections during the recent period of antimicrobial therapy, found that over 85 per cent of the complications had occurred in those patients with preoperative positive sputa Hughes,[5] in an experience of approximately 500 resections for tuberculosis, noted a tremendous increase in the percentage of complications when the tubercle bacilli were resistant

Robinson, Jones, Meyer, and Reding[6] reported their experience with surgery in 1363 tuberculous patients Of the nine with resistant bacteria, one died early and three late and all nine developed serious complications Wareham and co-workers[7] found a marked increase of persistent postoperative pleural spaces in the presence of drug resistant bacilli Of 71 resections in negative sputa cases, only three developed symptomatic pleural air spaces and all were cured by an ancillary surgical procedure, however, of 33 positive patients, 10 developed symptomatic air spaces which responded only poorly to subsequent surgical intervention Of these, three are dead, five remained active, and only two have been cured

Contrary to this extensive experience, Falk and Tucker[8] reported, in 1954, that bacterial resistance had little or no effect upon relapse or failure Likewise, Kukral[9] and coauthors state that, in the patient with isoniazid resistant catalase negative tubercle bacilli, the risk of serious postoperative spread of disease is minimal or absent

Recently, sputum positive and resistant cases have been subjected to definitive pulmonary resection with the aid and coverage of ancillary drugs Walkup and coauthors,[10] in 1952, reported the adjunctive use of viomycin in pulmonary surgery Three grams of the drug were given daily for 21 days in a series of 32 resections This regimen was of questionable value due to toxicity and a high incidence of postresection complications They suggested reducing the dosage and combining viomycin with other drugs In 1954, Murphy[11] recorded his experience with 13 patients in whom pulmonary resection was performed under PZA protection Though nine of the patients were resistant to streptomycin, the only complication was one postoperative bronchopleural fistula

Holland, Bell and Welles,[3] in 1955, reported resections under viomycin and terramycin protection on nine patients with cavitary lesions containing organisms resistant to streptomycin, INAH and PAS As three of these nine had major complications, they did not consider this combination promising

McLean and Benson,[12] in 1956, reported their experience with 24 patients considered "treatment failures" who were subjected to a viomycin-pyrazinamide program which lasted from two to 10 months. Viomycin was given in doses of one gram at 12-hour intervals two times per week and PZA was given in doses of one gram three times daily. About 50 per cent of these cases demonstrated some type of mild toxic reaction with a smaller percentage requiring discontinuance of the drug. In four patients with positive sputa and drug resistance, five pulmonary resections were performed early in the course of PZA-viomycin therapy (*third through the eighth week*). Two of the cases became inactive, one became sputum negative with stable "open negative" status, and the fourth relapsed on the fifth month after pneumonectomy for a destroyed lung. They recommend this combination for necessary surgery requiring additional drug protection and for acute exacerbations to minimize the extent of spread and necrosis.

It is the purpose of this study to analyze the surgical experience of 32 patients, with open positive lesions and bacillary resistance to streptomycin, INAH and PAS, who had resections under protection of viomycin-promizole and viomycin-PZA combinations.

Drugs

Viomycin,[13] produced by an actinomycete, although less active than streptomycin or isoniazid, is definitely more potent than PAS. Although toxic manifestations occur when viomycin is utilized daily, experience has indicated that, when used intermittently at two grams intramuscularly twice weekly, untoward reactions occur rarely and are generally mild.[14] Toxic manifestations may consist of auditory acuity loss, electrolyte imbalance, renal toxicity and skin eruptions.[15]

Pyrazinamide[16] is a potent synthetic antituberculosis agent, but when employed alone microbial resistance develops within a period of six to eight weeks.[17] Its use has been limited principally to seriously ill hospitalized patients with tuberculosis unresponsive to other agents. Four to 15 per cent of patients develop toxic manifestations,[18] particularly hepatitis and nonspecific symptoms including anorexia, nausea, vomiting, arthralgias, dysuria and fever. Pyrazinamide is usually given in doses not greater than 35 milligrams per kilogram a day and on the average of 500 milligrams *four times daily*.

Promizole, a synthetic heterocyclic sulfone compound,[19] is a relatively nontoxic agent which may be employed over a prolonged period.[20,21] Its most extensive uses have been in the treatment of miliary tuberculosis[22] and as a valuable adjunct to streptomycin for tuberculosis meningitis.[23] A daily dosage of one gram is started and increased to maintain a blood level of two to three milligrams per cent. Even at best, however, it must be classified as one of the weakest of present day tuberculostatic drugs. Its use in combination with viomycin for surgical protection in resistant open positive lesions has not been described heretofore.

Material

The present study is a review of 35 resections in 32 patients, all of whom had open positive lesions with bacilli proved or presumptively resistant to streptomycin, isoniazid and PAS Each patient was placed on viomycin in combination with promizole or with pyrazinamide for a two-week period preoperatively and this regimen was continued for approximately three months postoperatively The usual dosages administered were viomycin, two grams twice a week, promizole, one gram four times daily, and pyrazinamide, approximately 25 milligrams per kilogram or 500 milligrams four times daily During this period, streptomycin, PAS and isoniazid in the combinations which the patients had been receiving were maintained for whatever value they might possess

All patients were sputum positive within the six-weeks period immediately prior to surgery The patients were classified as resistant to these three drugs if cultural growth was not diminished by 10 micrograms of streptomycin, 10 micrograms of PAS or one microgram of isoniazid If the bacilli could not be cultured, those patients with open cavities and positive smears who had had chemotherapy for a minimum of one year were classified as presumptively resistant Only two in this total series had total therapy of less than one year and in both of these the bacilli were proved resistant by culture Only nine had been treated less than 18 months The others had received intermittent drug therapy up to seven years Thirty are retreatment cases, having had interrupted courses with two, or all three, of these drugs Again, the two who had not had interrupted courses of treatment were proved by culture to have resistant bacilli

The duration of total illness was likewise quite long as only 13 had had active pulmonary tuberculosis less than three years The others ranged up to 10 years since the initial onset of active pulmonary tuberculosis They varied in age from 18 to 60, with 18 being over 40 years of age Seventeen had previous collapse therapy, 10 having pneumoperitoneum, six, pneumothorax, and seven were thoracoplasty failures, one having had bilateral thoracoplasties One had a previous Monaldi procedure

Classification of disease by x-ray film standards on admission showed 28 had far advanced disease with four moderately advanced Classification by the last preoperative x-ray film showed 22 still remained far advanced and 10 moderately advanced No minimal lesion was encountered which met the criteria for inclusion in this particular series The contralateral lung was considered clear or minimal in only 16 cases, while 12 showed definite cavitation

The resections were of considerable magnitude in this group as 10 had pneumonectomies, 11 lobectomies, eight lobectomy plus segmental procedures and only three patients' resections were limited to segmental excisions, one of these being bilateral

Those with bilateral surgery had the following resections 1a) left upper lobe and b) apical posterior segments right upper lobe, 2a) right upper lobe and superior division right lower lobe and b) apical posterior

FIGURE 1A

FIGURE 1B

FIGURE 1C

FIGURE 1 B G, 54 year old white man Onset of pulmonary tuberculosis 1947 Thoracoplasty, 1949 Intermittent streptomycin and PAS since 1949 and INAH since 1953 Resection of left upper lobe and anteromedial basilar segment left lower lobe on March 1, 1956—*Figure 1A* Preoperative PA roentgenogram Note the consolidation opposite the apex of the heart—*Figure 1B* Preoperative laminogram showing large cavity beneath thoracoplasty—*Figure 1C* PA chest one year postoperatively

segment left upper lobe, 3a) apical posterior segment left upper lobe and b) apical posterior segments right upper lobe Another had a left decortication and resection of the right upper lobe and superior division right lower lobe

Indications for surgery In each case the residual lesion was already a collapse therapy failure (Fig 1) or thought inappropriate for collapse therapy In each instance there was an open cavity, often with evidence of bronchiectasis or bronchostenosis Nodular and fibrocaseous disease was present in virtually every case The lobes and lungs removed were usually caseified (Fig 2) or destroyed

Operative Findings The operations presented unusual technical difficulties due to severe degrees of hilar fibrosis and multiple enlarged and adherent lymph nodes surrounding the vessels and compressing the bronchi Operative hemorrhage occurred in four cases due to injury to the pulmonary arteries In each case it was possible to control this and complete the contemplated procedure

Results

There were four deaths in this series, none of which was related to the resistant bacilli or drug status One patient had a massive pulmonary embolus while on the operating table. A second died on the 20th postoperative day from pulmonary emboli proved by autopsy The third death occurred from pulmonary circulatory insufficiency six days after resection of the left upper lobe and superior division of the left lower lobe and plombage thoracoplasty At autopsy, the contralateral pulmonary artery

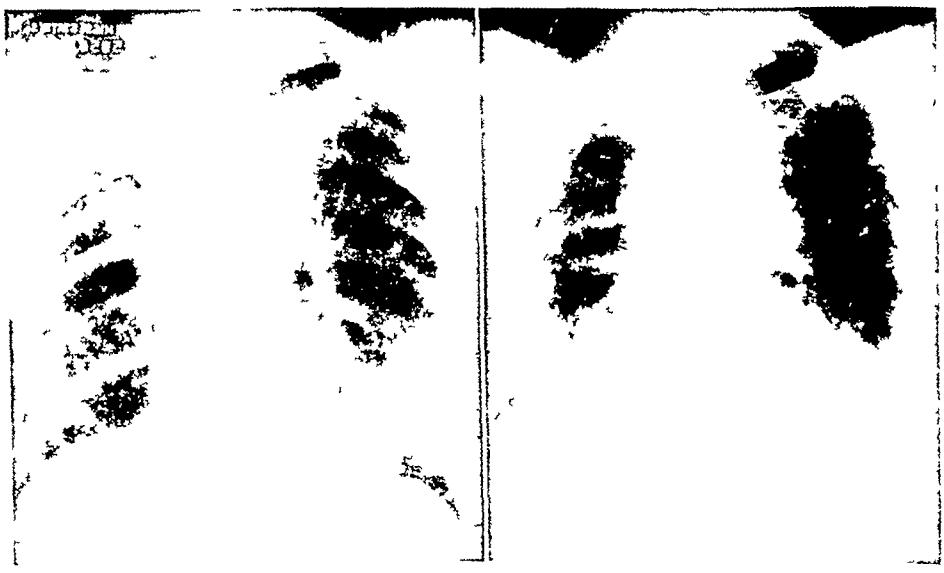


FIGURE 2A FIGURE 2B

FIGURE 2 A G, 51 year old white man Onset of disease 1948 Intermittent streptomycin and PAS since 1951 and INAH since 1953 Resection of consolidated right upper lobe with 5 cm cavity October 18, 1956—*Figure 2A* Preoperative PA roentgenogram chest—*Figure 2B* PA chest, following resection of right upper lobe and tailoring thoracoplasty Sputa negative

was found to be almost totally occluded by a large arteriosclerotic plaque thought to be an old organized thrombus The fourth patient died of myocardial failure with pulmonary edema on the first day after resection of the destroyed right lung Autopsy revealed enlargement of the heart with extensive acute "myocardosis"

There was no bronchopleural fistula, empyema or postoperative spread but two early reactivations did occur (Chart 1) One had reactivation of a small area of former disease in the contralateral base one month postoperatively which has been controlled by pneumothorax now discontinued after two and one half years The sputa have remained consistently negative The second had reactivation of a residual lesion in the contralateral upper lobe three weeks after pneumonectomy for a destroyed lung *One culture was positive five months following operation, but the bacteriology has been negative for the subsequent six months and the x-ray film* shows continued improvement

Of the 28 remaining patients which have been followed from six to 36 months, 26 are negative bacteriologically with stable x-ray films (Chart II) Six were treated with viomycin and promizole and five of them are classified as arrested or inactive at this time The sixth had had bilateral plombage thoracoplasties which failed to accomplish permanent *sputum conversion The superior division* of the left lower lobe was resected for a residual cavity but eight months later the sputum again became positive and the x-ray film revealed reactivation in the right lower lobe Six months later his x-ray film shows continued clearing and his sputa are negative

Of the 26 patients resected under viomycin and pyrazinamide protection, four are dead as noted and 21 are arrested or inactive at this time One

CHART I
COMPLICATIONS—TB

	Vio-Prom	Vio-PZA
Early Reactivations	0	2
Late Reactivations	1	0
Bacterial Relapse (late)	0	3 (Temporary)

CHART II
PRESENT STATUS

	Patients	Active	Inactive	Dead Non TB
Vio-Prom	6	1	5	0
Vio-PZA	26	1	21	4
TOTAL	32	2	26	4

mentioned above required a postoperative contralateral pneumothorax for early reactivation Three had a single positive sputum at three, four and four months respectively after operation but they have been negative for 12, 14 and 15 months respectively now with stable x-ray films shadows

Other Complications (Chart III) There was one postoperative hemothorax which was cleared successfully by enzymatic debridement One had a temporary cardiac arrest during the operative procedure The heart returned to normal rhythm after only a few seconds of massage and the resection was completed without further incident

Postoperative tracheostomies were performed in six patients In all of these, retained secretions were a major factor In two, however, definite respiratory insufficiency was encountered which further influenced the decision for the tracheostomy One of these patients had to be maintained on artifical respiration for six days postoperatively but has subsequently returned to an asymptomatic status except for dyspnea on moderate exertion

Toxicity Only one patient had to have viomycin discontinued because of persistent rash and itching No severe toxic manifestation was noted to pyrazinamide but one patient had to have piomizole discontinued due to recurrent rash

Discussion

At this time, many patients are found to have open positive tuberculous lesions with bacilli proved or presumptively resistant to streptomycin, isoniazid and PAS Some of the patients in our series are sanatorium failures accumulated during the developmental stages of our present concepts of antibiotic therapy and of the timing of definitive surgery Obviously many had drug regimens completely inadequate by present day standards and the optimal time for surgery was missed Another important factor in this regard was found to be the increasing trend toward home treatment where supervision is necessarily less complete than in sanatoria Seventeen of the above 32 patients entered the sanatorium after resistance had already developed during treatment elsewhere

It is our belief that this group of patients became resistant because of various mechanical obstructing factors which tended to keep cavities open Hilar fibrosis and extensive peribronchial lymphadenopathy produced bronchiectasis, bronchostenosis, tension cavities and carnified parenchyma These would prevent cavity closure regardless of the nature

CHART III
COMPLICATIONS—NON TB

Hemothorax	1
Cardiac Arrest	1
Tracheostomy for Secretions	6
Respiratory Insufficiency	2

of antibiotic therapy employed and thus allow the development and persistence of resistant bacilli

These patients offer a tremendous challenge both in evaluation and in treatment In recent years, our goals in tuberculosis therapy have shifted from being satisfied with the development of the "good chronic" with quiescent disease to the constant striving for attainment of the inactive state As these patients are complete medical failures, surgery is frequently attempted in desperation as the only hope for these "salvage" cases We have utilized plombage thoracoplasties in such patients with gratifying results whenever the lesion is amenable to collapse therapy In the many patients, however, who are already thoracoplasty failures, or who have cavitied disease or advanced bronchial destruction, only resection can offer reasonable hope of success

As noted above, resection in the face of resistant bacilli is usually accompanied by a forbidding morbidity rate Our results of resection under the temporary umbrella of viomycin and promizole or pyrazinamide indicate that this salvage surgery can be performed without undue complications even in the presence of bacilli resistant to streptomycin, isoniazid and PAS Due to the extensive and bilateral involvement of these cases, undoubtedly many will have poor ultimate prognoses

We have not used promizole recently since pyrazinamide, the more potent drug, has been available at a reasonable cost With the more recent addition of cycloserine to our armamentarium, another "sprinter" drug is available for temporary coverage Streptovarcin has not at this time been fully evaluated for its potential role, but likewise appears promising

In view of modern knowledge of the bacteriology of the tubercle bacillus with its predilection for early resistance to any one of the known therapeutic agents, and the delaying or prevention of this phenomenon by the combination of a second drug, there does not seem to be any logical reason for using one drug whenever two are available In many instances, the source of the positive sputum and thus the resistant bacilli have been removed at the time of surgery If no immediate untoward reaction occurs from spillage of resistant bacilli or from uncontrolled endobronchial disease at the level of bronchial transection, the results should be favorable as the remaining bacilli may well be sensitive to the usual drugs In salvage cases, however, where there has been extensive and bilateral involvement, particularly with cavitation, the prognosis for good long-term results must remain guarded

SUMMARY

1) An analysis is presented of the temporary protection of viomycin combined with promizole or pyrazinamide in 35 pulmonary resections in 32 patients with open positive tuberculous lesions In each, the tubercle bacilli were proved or presumptively resistant to streptomycin, PAS, and isoniazid

2 The failure of previous medical therapy was found to be explained by mechanical factors which would prevent cavity closure regardless of the nature or duration of medical therapy

3) There were four deaths unrelated to drug coverage There has been no spread, bronchopleural fistula or empyema Two patients had early and one a late reactivation Three additional patients demonstrated late bacteriologic relapses, but have subsequently been negative over a year Thus, of 28 survivors followed from six to 36 months, 22 have never shown postoperative activity and 26 may now be classified as arrested or inactive

4) Viomycin combined with either promizole or pyrazinamide appears to offer satisfactory temporary protection for excisional surgery in tuberculosis Nonetheless, promizole has not been used since the availability of the more potent pyrazinamide

RESUMEN

1 Se hace un análisis de la protección temporal que produce la Viomicina asociada al promizol o pirazinamida en 35 resecciones pulmonares realizadas en 32 enfermos con lesiones tuberculosas abiertas y bacilíferas En cada uno se demostró que el bacilo era resistente (o se presumió que así era) a la estreptomicina, el PAS y la isoniacida

2 El fracaso del tratamiento previo pudo explicarse por factores mecánicos que evitarían la clausura de la cavidad cualquiera que fuese la naturaleza y la duración del tratamiento médico

3 Hubo tres defunciones sin relación con el uso de la droga No hubo diseminaciones, fístula broncopleural o empiema Dos enfermos tuvieron reactivación, uno temprana y otro tardía Dos enfermos más presentaron recaída bacteriológica tardía pero después se hicieron negativos por más de un año Así, de 28 sobrevivientes observados de seis meses a 36 meses, 22 no han tenido actividad patológica postoperatoria y 26 se han clasifcado ya como detenidos o inactivos

4 La viomicina combinada ya sea con promizol o con pirazinamida parece ofrecer una protección temporal satisfactoria para la cirugía de excisión en entuberculosis Sin embargo, el promizol ha dejado de usarse desde que se puede obtener un agente más potente como es la pirazinamida

ZUSAMMENFASSUNG

1 Es wird eine Analyse vorgelegt über den temporären Schutz von mit Promizol oder Pyrazinamid kombinierten Viomicyn bei 35 Lungenresektionen an 32 Kranken mit offenen, positiven tuberkulosen Befunden Bei jedem dieser Falle waren die Tuberkelbazillen nachgewiesener Massen oder vermutlich resistent gegen Streptomycin, Pas und INH

2 Die Erklarung fur das Versagen einer vorausgegangenen internen Behandlung wurde in mechanischen Faktoren gefunden, die einen Kavernenverschluss verhinderten unbeschadet der Art und Dauer der konservativen Therapie

3 Ohne Bezug auf den medikamentosen Schutz traten 4 Todesfalle ein Es kam zu keiner Aussaat, inneren Fistel oder Empyem 2 Patienten bekamen eine fruhzeitige und einer spate Reaktivierung 3 weitere Kranke erwiesen spate bakteriologische Ruckfalle, waren aber anschliessend mehr als ein Jahr negativ Demnach haben von 28 Überlebenden, deren Verlauf 6-36 Monate lang weiter verfolgt wurde, 22 zu keiner Zeit eine postoperative Aktivitat an den Tag gelegt und 26 konnen jetzt als stillstehend oder negativ gekennzeichnet werden

4 Viomycin in Verbindung entweder mit Promycol oder Pyrazinamid scheint einen befriedigenden temporaren Schutz zu bieten fur die Resektionsbehandlung bei der Tuberkulose Nichtsdestoweniger ist Promizol nicht mehr verwandt worden, seitdem das starker wirksame Pyrazinamid zur Verfugung steht

REFERENCES

1 Coleman, F P and Bunch, G H, Jr "Is Pulmonary Resection Safe in the Patient Previously Treated with Streptomycin?" *Am Sixth Streptomycin Conf*, 6 146, 1948

2 Murphy, J D "A Study of the Factors Influencing the Success of Segmental Resection for Pulmonary Tuberculosis," *Trans Nat Tuberc, Assn 50th Ann Meeting*, p 264

3 Holland, R H, Bell, J W and Welles, E S "Pulmonary Resection in Active Cavitary (Open-Positive) Tuberculosis," *J Thoracic Surg*, 31 83, 1956

4 Lees, W M In Discussion of Holland, R H, Bell, J W and Welles, E S "Pulmonary Resection in Active Cavitary (Open-Positive) Tuberculosis," *J Thoracic Surg*, 31 83, 1956

5 Hughes, F A, Jr In Discussion of Holland, R H, Bell, J W and Welles, E S "Pulmonary Resection in Active Cavitary (Open-Positive) Tuberculosis," *J Thoracic Surg*, 31 83, 1956

6 Robinson, J L, Jones, J C, Meyer, B W and Reding, F S "The Surgery of Pulmonary Tuberculosis," *Am. Rev Tuberc*, 73 690, 1956

7 Wareham, E E, Barber, H, McGoey, J S and Miscall, L "The Persistent Pleural Space Following Partial Pulmonary Resection," *J Thoracic Surg*, 31 593, 1956

8 Falk, A and Tucker, W B "Resection Failures in Pulmonary Tuberculosis," *Trans Nat Tuberc Assn 50th Ann Meeting*, p 254, 1954

9 Kukral, A J, Grow, J B, Middlebrook, G and Dressler, S H "The Handling of the Poor Risk Patient with Pulmonary Tuberculosis Antimicrobial Therapy, Cardiopulmonary Function and Surgery," *Dis Chest*, 29 226, 1956

10 Walkup, H E, Murphy, J D and Kanner, O "The Use of Viomycin with Excisional Surgery for Pulmonary Tuberculosis," *Trans 11th Conf Chemother Tuberc*, 11 127, 1952

11 Murphy, J D "A Six-Year Review of the Use of Chemotherapy in the Surgical Treatment of Pulmonary Tuberculosis," *J Internat Coll Surg*, 21 88, 1954

12 McLean, R L and Benson, W P "Viomycin and Pyrazinamide in Far Advanced, Drug Resistant Pulmonary Tuberculosis," *Trans 15th Conf Chemother Tuberc*, 15 122, 1956

13 Finlay, A C, Hobby, G L, Hochstein, F, Lees, T M, Lenert, T F, Means, J A, P'an, S Y, Regna, P P, Routien, J B, Sobin, B A, Tate, K B and Kane, J H "Viomycin, A New Antibiotic Active Against Mycobacteria," *Am Rev Tuberc*, 63 1, 1951

14 Pitts, F W, O'Dell, E T, Dye, W E, Hughes, F J, Jr and Tempel, C W Intermittent Viomycin Therapy in Pulmonary Tuberculosis," *Trans 11th Conf Chemother Tuberc*, 11 270, 1952

15 Pitts, F W, O'Dell, E T, Howard, O P, Schmidt, C H, Chambers, J S "Clinical and Laboratory Toxicity Encountered During Intermittent Viomycin Therapy," *Trans 11th Conf Chemother Tuberc*, 11 279, 1952

16 Schwartz, W S and Moyer, R E "Pyrazinamide (Aldinamide) in the Effect of Tuberculosis A Preliminary Report," *Trans 11th Conf Chemother Tuberc*, 11 302, 1952

17 Yeager, R L, Munroe, W G C and Dessau, F I "Aldinamide, Experience in the Treatment of Pulmonary Tuberculosis," *Trans 11th Conf Chemother Tuberc*, 11 298, 1952

18 Livings, D G "Pyrazinamide and Isoniazid Summarized Data from V A-Army-Navy Coop Study," *Trans 15th Conf Chemother Tuberc*, p 101, 1956

19 Bambas, L L "Some Chemotherapeutically Active Sulfones II," *J Am Chem Soc*, 67 671, 1945

20 Feldman, W H, Hinshaw, H C and Mann, F C "The Effect on Experimental Tuberculosis of Promizole A Preliminary Report," *Proc Staff Meet, Mayo Clin*, 19 25, 1944

21 Hinshaw, H C, Feldman, W H and Pfuetze, K H "The Clinical Administration of Promizole in Tuberculosis A Preliminary Report," *Proc Staff Meet, Mayo Clin*, 19 33, 1944

22 Milgram, L, Levitt, I and Una, M S "Promizole Treatment of Miliary Tuberculosis," *Am Rev Tuberc*, 55 144, 1947

23 Lincoln, E M, Kirmse, T W and DeVito, E "Tuberculous Meningitis in Children A Preliminary Report of its Treatment with Streptomycin and Promizole," *J A M A*, 136 593, 1948

Echinococcus Cyst of the Lung

MILTON GINSBERG, M D , JOSEPH M MILLER, M D
and JOHN A SURMONTE, M D *
Fort Howard, Maryland

Since patients with echinococcus cysts of the lungs are rarely seen in the United States, this report is made to alert those interested in diseases of the chest, to include that due to Echinococcus granulosus in differential diagnosis of pulmonary lesions Infestation with echinococcus is common in Iceland, parts of central Europe, Italy, Africa, South America, Australia, New Zealand, Syria, Arabia, Siberia, Turkestan, the northern part of China, Japan and the Republic of the Philippines These areas closely parallel the theaters of operation of World War II The incidence of disease due to echinococcus may increase in the United States because large numbers of veterans of the armed forces have served in these areas Therefore, the diagnosis and treatment of this disease should assume greater importance than it has in the past

The common definitive hosts are dogs, wolves, jackals, coyotes and other canidae The usual intermediate hosts are sheep, cattle, horses, other herbivorous animals, and hogs [6] The moose has also been shown to be an intermediate host [12] In northern Canada and most of British Columbia, the herbivora, usually the moose or caribou, may serve as intermediate hosts [11] Infestation of man is accidental and ordinarily by ova in the feces of dogs

Infection with echinococcus in all anatomical sites and in the lungs varies geographically (Table I) The number of patients in the United States and Canada (Table II) has not approached that seen in certain other parts of the world As near as can be determined, the total number of patients with involvement of the lungs in the United States and Canada is 166 (Table III) The patient reported by Evans[15] was previously described by Benson, Evans and Zuelger [7] The report of Miller,[36] however, is surprising Ninety-seven patients with cysts in the lungs have been found in Canada with the diagnosis having been made in the previous five years from hospital records and roentgenograms of the chest Miller[36] was certain that all patients, in whom the diagnosis was made by roentgenogram had hydatid cysts The roentgenographic shadow was characteristic, however, particularly since roentgenograms taken in successive years showed a gradual increase in size of the area of disease Miller[36] was reasonably sure that a correct diagnosis was made in 90 per cent of the patients More patients with pulmonary hydatid disease in Canada have been reported by Miller[36] than have been known to exist in the the United States and Canada previously The present instance makes the total number of patients reported from the United States and Canada, as far as can be determined, 167

*Surgical Service, Veterans Administration Hospital

Three with hydatid disease of the lungs always lived in the United States as reported by Garrett,[18] the first of Phillips,[40] and of Johnson and Twente.[27]

The symptoms of echinococcus disease of the lungs are few and are not pathognomonic. Generally, the patients are healthy. Early symptoms are cough, slight hemoptysis, and transient episodes of elevation of temperature. Pain in the chest is not present unless the cyst is in contact with the pleura. In a review of 478 persons with pulmonary hydatid disease in New Zealand and Australia, Waddle[57] reported that a latent period of years may exist between the time of infection and the appearance of any symptom. The presence of a hydatid cyst becomes suspected frequently only when a complication, such as leakage, frank rupture, or bacterial infection ensues. The cyst may rupture into a lung and the contents are coughed up or rupture into the pleural space and cause empyema.

Eosinophilia is totally unreliable in the diagnosis of echinococcus infection. Moreover, it is not present in persons with cysts which have undergone suppuration or death.

Rupture of cysts into bronchi may occur and scolices, hooklets, and pieces of the laminated membrane may be coughed up. Microscopic identification of any or all of these elements offers a positive method of diagnosis.

Three diagnostic immunological reactions have been studied at length. These include the complement fixation test, the intradermal test, and the precipitin test.

Ghedini,[19] in 1907, first applied the complement fixation test, or the

FIGURE 1 FIGURE 2

Figure 1 Postero-anterior roentgenogram of the chest showing homogenous mass in the upper part of the left lung on February 15, 1951.—*Figure 2* Left lateral roentgenogram of the chest after a swallow of barium showing homogenous mass in the upper part of the left lung on February 15, 1951

Bordet-Gengou method of serologic diagnosis, to echinococcus disease. It is a good diagnostic test. Fairley[9] demonstrated that a positive result depended upon whether the hydatid was alive and whether communication existed between the cyst and the host. In 45 uncomplicated cysts, where apparently a good wall was still present, a positive result was obtained in 21, (75.6 per cent) and a negative in 11, (24.4 per cent). With recent incomplete rupture of the cyst wall, 12 patients gave positive results in 11 (91.7 per cent) and a negative in one. With recent suppuration and apparent free communication between the cyst and the host, positive results were obtained in 17, (100 per cent). With death of the parasite as in two patients with chronic suppuration, three with old complete rupture, and 11 with degeneration of the parasite, negative results were

TABLE I

Authors	Year of Report	Geographical Location	Per Cent of Patients With Involvement Of Lungs
Thomas	1891	Australia	11.5
Perper	1903	Germany	10.6 to 11.9
Deve[1]	1912	France	8.5
Fairley[1]	1922	Australia	13
Magath[10]	1921-1922	United States and Canada	5.4
Dew[11]	1928	Australia	12.5
Loucks[1]	1930	North China	6.25
Barnett[2]	1935	Australia	17.3
Magath[5]	1937	United States and Canada	6.8
Godfrey[7]	1937	Australia	12.5
Arce[1]	1941	Argentina	15
Rivas, Gobich and Mantilla[13, 14]	1944	Argentina	20.8
Davidson[1]	1944	World	10
Babcock[2]	1944	World	10 to 15
Strong[21]	1944	Endemic Areas	As much as 12
Cole[11]	1945	Australia and New Zealand	24.5
Barrett[4]	1947	Australia	25
		France	9
Miller[36]	1953	Canada	69
Jidejian[ ]	1953	Lebanon	28
Susman[21]	1953	Australia	23
		Iceland	1.5

obtained in 100 per cent In a series of 83 with living hydatid cysts, positive reactions were obtained in 70, (84 3 per cent), and a negative in the remainder

The intradermal test reported by Casoni[9] is generally reliable although occasionally false positive reactions are obtained Fairley and Kellaway[17] believe that a positive Casoni test is of diagnostic value only in patients who never had an operation for a hydatid cyst In such patients, the response was found in about 75 per cent of those with uncomplicated or degenerating cysts When the test was done routinely on patients in whom hydatid disease was suspected, failure to react indicated the absence of disease in at least 95 per cent A positive result was not significant in the diagnosis of recurrent or residual cyst In 1952, Barrett and Thomas[3] reported the test to be generally reliable but a positive reaction was obtained in a small group of patients with carcinoma, particularly with multiple secondary deposits The Casoni reaction does not change quickly or certainly from positive to negative and may be positive for five or more years in a patient without persisting infestation The reaction cannot be used as a guide to cure of any specific lesion or to indicate the presence of other hidden cysts Rose and Culbertson,[14] in 1939 pointed out that the supply of fluid for use in the Casoni test is poor throughout North America thus creating difficulty in diagnosis Four patients known to have hydatid disease gave an *immediate positive reaction*, however, with an antigen prepared from Taenia pisiformis found in the rabbit In 1940, Rose and Culbertson[16] stated that the Casoni test and the complement fixation test were apparently group specific rather than species specific Antigens made from Cysticerous pisiformis found in the rabbit and Taenia taeniaformis found in the cat could be substituted for hydat d fluid

FIGURE 3 Scolices of the Echinococcus granulosus

Weinberg,[58] in 1913, reported a study on the use of the precipitin test which is less accurate than the complement fixation test and the intradermal test Strong,[51] in 1944, stated that a positive reaction with the precipitin test was obtained frequently if the antigen was good but false positive reactions occurred

Jidejian[25] reported that the slow exchange of substances between the host and the contents of the cyst was responsible for the intoxication, the allergy, and the antibody formation in the host This exchange was the cause of the eosinophilia, the Weinberg reaction, and the Casoni reaction Positive results from all of these laboratory tests may be absent in a patient with a hydatid cyst In addition, positive tests may become negative with a denser and less permeable cyst wall An operation resulting in cure produces a rapid disappearance of the eosinophilia, the Casoni test, and the Weinberg reaction Dead cysts do not produce antigen and if sufficient time has elapsed since the death of the cyst, all circulatory antibodies will disappear and all of the tests mentioned will become negative

Aspiration for diagnosis should not be done since, if hydatid fluid containing scolices is spilled, new cysts may form In addition, empyema may result Aspiration should not be used in the clinical investigation of moderately large or large round lesions of the lung of unknown etiology

A round homogenous shadow in the pulmonary parenchyma is seen in the roentgenogram of the chest of a patient with an echinococcus cyst of the lung According to Santy, Berard, and Sournia,[47] when the patient is prone, has the head tilted down, and has taken a deep breath, fluoroscopy showed a transverse lengthening of the cyst as if it responded to the widening of the chest The authors point out, however, that this is only a sign of any cyst

Arce[1] has described the changes in the roentgenogram when the cyst

TABLE II

Authors	Year of Report	Geographical Location	Patients In All Anatomical Locations	Patients With Involvement of Lungs
Osler[37]	1892	America	61	5
Osler[38]	1892	United States and Canada	85	6 (Lung or Pleura)
Sommer[49]	1895	America	67	5
Sommer[50]	1896	America	100	7
Lyon[32]	1902	North America	241	11
Magath[34]	1922	North America	334	15
Magath[35]	1937	Canada and United States	482	32

comes into contact with a bronchus A small amount of air may go between the membrane of the parasite and its adventitia and the air appears in the shape of a cap and gives rise to perivesicular pneumia If an opening into the membranes occurs, a part of the fluid may be expelled and air finds its way between the adventitia and the membrane and between the membrane and the remaining fluid Two air chambers are seen to form the double arch sign described by Ivanissevich[24] With marked tearing or total disintegration of the cystic membrane, a cap of air and a dull, movable horizontal shadow, which is the hydatid fluid upon which the cystic membranes float, forms the water-flower sign

The operation for hydatid cyst has undergone considerable modification particularly since the newer advances in thoracic surgery have been made[1 4 5 10 12 25 29 31 41 52-54, 57] Surgery should be conservative, should be undertaken early to avoid complications, and should include removal of the parasite, avoidance of contamination of the wound and the pleural cavity with live hydatid elements, provision for dealing with the sac in the lung, and removal of diseased parenchyma of the lung

Opinion as to the injection of formalin into the cyst before opening it or swabbing the cyst with formalin after evacuation varied The chemical was used frequently, Barrett[4] and Waddle[57] pointed out that the injection of formalin was not a good procedure

Waddle[57] and Barrett and Thomas[5] have reported large series of patients with pulmonary hydatid disease who were subjected to surgery The

FIGURE 4

FIGURE 5

Figure 4 Postero-anterior roentgenogram of the chest showing the cyst with the membranes floating on the fluid on February 21, 1951 —*Figure 5* Left lateral roentgenogram of the chest showing the cyst with membranes floating on the fluid on February 21, 1951

type of operation varied according to the state of the disease present in the patient and the results were excellent

Case Report A 26 year old Negro, admitted to the surgical service of the hospital on February 15, 1951, had mild pain in the chest and cough, which was not productive, for about four days The pain was sudden in onset involving the right and left sides of the chest at first but soon localizing to the left anterior thoracic region (A history of hemoptysis, poor appetite, and loss of weight was not obtained) He was referred for treatment when a mass in the left lung was discovered on the roentgenogram of the chest

He had served in apparently good health in the African and in the Italian campaigns during World War II

His temperature on admission was 99° F The breath sounds were distant throughout both lungs and absent over the left anterior chest Moist rales were heard in both lungs The remainder of the physical examination was normal

The hemoglobin was 12 1 grams per 100 cc and the leukocyte count 6,050 per cmm of which 68 per cent were polymorphonuclear neutrophilic leukocytes, 31 per cent lymphocytes, and 1 per cent polymorphonuclear eosinophilic leukocytes The serologic test for syphilis was negative Acid-fast bacilli were not found in the sputum

A shadow of a round homogenous mass about nine cm in diameter was seen in the upper part of the left lung on the postero-anterior roentgenogram of the chest (Figure 1) An ovoid contour was observed in the left lateral position (Figure 2) Bronchoscopy revealed a moderate degree of compression of the left main bronchus about two cm below the carina by an extrinsic mass The remainder of the examination was normal

A 22 gauge needle was inserted into the involved area in the fourth interspace in the anterior axillary line and about 300 cc of crystal clear fluid were aspirated It was then suspected that the patient had an echinococcus cyst Examination of the fluid showed scolices of Echinococcus granulosus (Figure 3)

The postero-anterior and lateral roentgenograms of the chest taken after the aspiration showed a large cyst with a fluid level The membranes of the cyst could be seen floating on the fluid (Figure 4) On the same day an increase in temperature occurred A peak of 102 8° F was reached in about four days and it returned to normal in about six days

The roentgenograms of the chest showed an opaque area below the cyst interpreted as pneumonitis The area of infiltration disappeared in about 10 days under treatment with penicillin and aureomycin

TABLE III

Authors	Year of Report	Geographical Location	Patients With Involvement of Lungs
Phillips[41]	1934	North America	36
Lilienthal[11]	1934	United States	1
Johns[36]	1934	United States	1
Haight and Alexander[1]	1940	North America	46
Benson, Evans and Zuelger[7]	1943	United States	1
Holman and Pierson[31]	1944	United States	2
Davidson[12]	1944	United States	3
Brewer III, Jones and Dolley[5]	1948	United States	1
Tucker[56]	1951	United States	1
Johnson and Twente[32]	1952	United States	1
Miller[38]	1953	Canada	97
Keigin[28]	1953	Canada	1 (Total unknown)
Harrison[20]	1953	Canada	11
Seley[48]	1953	United States	2